Ibuprofen and Paracetamol: Relative Safety in Non-prescription Dosages

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Much interest has recently been shown in the safety of non-narcotic analgesics and non-steroidal anti-inflammatories (NSAIDs) when used under non-prescription (i.e. 'over-the-counter' or OTC) conditions. In North America some NSAIDs, for example, naproxen and ketoprofen, hitherto available only on prescription have, in the last year or so been granted permission for sale OTC. Ibuprofen was the first non-aspirin NSAID to be allowed for OTC sale and has been sold as such for over a decade in many countries of the world. In many respects the granting of permission by the UK Committee on the Safety of Medicines (CSM) in 1983 and the US Food and Drug Administration (FDA) in 1984 to allow the sale direct to the public of ibuprofen OTC represented a milestone in the attitudes of these drug regulatory authorities. The approval by the FDA and the CSM was based essentially on the substantial safety record of this drug in the higher, prescription doses used for the treatment of rheumatic and other chronic and acute painful conditions (Paulus 1990). Before the approval for ibuprofen OTC sale, the various formulations of aspirin and other salicylates, and the fenamates (indicated for menstrual pain), were the only NSAIDs available OTC. Also, the non-narcotic analgesics (i.e. non-NSAIDs) used OTC world-wide for the treatment of pain comprised paracetamol, and (before its withdrawal) the pro-drug of paracetamol, phenacetin, as well as antipyrine, aminopyrine and their congeners. Paracetamol, was only approved in the UK in 1955 for non-prescription use and marketed for OTC use in 1956, and along with aspirin this was the drug mostly used by the lay public for self-medication of pain, until the advent of ibuprofen for OTC use (Prescott 1992). The use of ibuprofen has increased substantially in the past decade, and recently paediatric formulations of this drug (e.g. Junifen) have been approved for OTC sale in several countries. It is, therefore, of interest to assess the relative safety and efficacy of these drugs compared with other NSAIDs and OTC analgesics.

Aspirin has had a long history of use by the lay public since its introduction nearly a century ago and in many respects the safety issues are well understood. The major adverse effects of concern with this drug are the well-known propensity to cause ulceration and bleeding from the gastrointestinal tract (Rainsford & Quadir 1995). Even at the lowest dosage recommended for prophylaxis of coronary vascular conditions (30–75 mg daily or 325 mg every other day) there is statistically significant, even if low, incidence of severe gastrointestinal adverse events (Steering Committee of the Physicians' Health

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Study Research Group 1989; The Dutch TIA Trial Study Group 1991; The SALT Collaborative Group 1991). Paracetamol is generally regarded as having a low incidence of symptoms of gastrointestinal ulceration and bleeding (Prescott 1992) and in studies of experimental models of animals and man is usually regarded as a bench standard for low or non-ulcerogenicity. The extensive pharmacoepidemiological studies and adverse drug reaction reports to the major drug regulatory authorities world-wide indicate with some exceptions (Bidlingmaier et al 1995) that ibuprofen has the lowest incidence of gastrointestinal ulceration and bleeding among the NSAIDs at the higher prescription doses used for the therapy of rheumatic and other chronic painful diseases (Rainsford & Quadir 1995). Thus, ibuprofen at OTC doses is likely to have a lower incidence of gastrointestinal adverse events when examined on a population basis, but there has been no detailed attempt to review this situation. It is, therefore, of importance to establish if this drug results in any appreciable incidence of adverse effects in the gastrointestinal tract at OTC doses especially in comparison with paracetamol, the drug, other than aspirin, mostly used by the public for pain control.

Thus, in this review we have surveyed the literature on adverse reactions to both paracetamol and ibuprofen, and analysed in detail the published data on adverse reactions reported in clinical trials performed specifically under OTC dosage conditions. We have compared ibuprofen with paracetamol at their respective OTC dosages, and studied safety data from reports where these drugs have been compared with placebo, or other analgesics and NSAIDs. Being aware that the major adverse reports are likely to have involved the gastrointestinal system we have given particular attention to analysis of gastrointestinal adverse reactions. In the absence of any substantial data from drug regulatory authorities on voluntary or compulsory reporting of adverse drug reactions, this is probably the best available data likely to be available world-wide to indicate the relative safety of these drugs. This is because OTC data are not always reported to drug regulatory authorities. We have also sought to establish the relative efficacy of these drugs from the published reports. An issue of importance is whether the added anti-inflammatory property of ibuprofen mediated through its prostaglandin inhibition or from direct effects on neural pathways of pain (Jurna 1991; Rainsford 1996a, b) confers added pain-relieving effects at OTC doses in comparison with that of OTC paracetamol. It has also been shown that paracetamol might have different mechanisms of analgesia, especially in the central nervous system compared with those of NSAIDs (Urquhart 1994). Another aspect is whether there are differences in the patterns

of use of these two drugs in different pain states and this has also been considered, so that assessments of safety might be viewed in relation to the effectiveness in different pain conditions.

Adverse Reactions and Toxicology

Before considering the detailed published reports of adverse reactions at OTC doses it is useful to consider the global reports of adverse reactions to ibuprofen and paracetamol (i.e. from prescription use of these drugs), the general toxicological profile of these drugs, and the possible mechanisms underlying the development of adverse reactions and toxicological effects of these drugs.

In considering the toxicity of NSAIDs and non-narcotic analgesics such as paracetamol, it is important to recognize that these adverse reactions can be classified as Types A, B or C. Type-A reactions are an exaggerated response to intrinsic pharmacological properties (e.g. effects secondary to the inhibition of prostaglandin synthesis for initiation or promotion of gastrointestinal bleeding, bronchospasm and asthma, renal papillary necrosis and salt-water retention, cardiovascular complications including exacerbation of hypertension and decreased efficiency of diuretics and β-adrenergic receptor antagonists). Type-B reactions are bizarre and unexpected, usually of low frequency, and result from abnormal handling of the drug by the patient or an idiosyncratic immunological response (e.g. anaphylaxis, skin reactions, fever, lymphadenopathy, thrombocytopenia, agranulocytosis, leucopenia, aplastic anaemia, haemolytic anaemia, cholestatic jaundice and hypersensitivity hepatitis, renal failure and interstitial nephritis, vasculitis and sialadenitis). Type-C reactions are those that are not known to be related to actions of the drug (Fowler 1987). Type-A reactions occur with relatively high frequency and so can usually be identified in Phase II and Phase III clinical trials and during the period after introduction of the drug. It is during the period up to 2 years after introduction of NSAIDs that there is often a high frequency of reporting of these Type-A reactions (Weber 1984). This high frequency has been attributed to increased awareness of reporting of drugs to those agencies which have voluntary reporting schemes, influences of marketing creating greater awareness of the new drug, and a period of understanding how to use the drug and appreciating its side-effects (Weber 1984). This high frequency of reporting has been described as 'the Weber effect' after Dr Weber of the UK Committee on Safety of Medicines, who first identified this phenomenon (Weber 1984).

Type-B reactions are typically idiosyncratic; because they occur in low frequency there are problems about the statistics of the occurrence of these rare events. Thus, an idiosyncratic reaction with a frequency of 1 in 10 000 requires the treatment of 30 000 subjects to give a 95% confidence limit around the estimate of risk (Fowler 1987). Even after the immediate post-marketing phase during which the Weber effect would be evident, low-frequency idiosyncratic reactions, even if they are severe, would be unlikely to be reported. It is, then, only after long-term exposure of man to the drug that these rare idiosyncratic reactions occur. For the purposes of this review we have seen exposure of a variety of populations throughout the world to ibuprofen and paracetamol for such a long period of

time since their introduction (ibuprofen 1969; paracetamol since its re-introduction without prescription in 1955 (Nicholson 1982; Busson 1986; Prescott 1992)) that these rare Type-B reactions can probably be determined at defined frequencies.

Adverse reactions and toxicology of paracetamol

The adverse reactions occurring with paracetamol probably have not been reported in the same way as the formal reports of NSAIDs such as ibuprofen. At the time of its introduction in the USA and the UK in the mid-1950s paracetamol was primarily indicated for acute conditions such as fever and pain and reports of adverse reactions were relatively few; it was generally believed that this was a remarkably safe drug (Prescott 1992). Indeed, the strikingly low incidence of gastrointestinal side-effects can be contrasted with those of aspirin which was then, and in subsequent years, of major concern because of the high incidence of associated gastrointestinal ulceration and bleeding (Prescott 1992). The extensive studies which have subsequently been performed with paracetamol in man and in animal models, and in various clinical investigations, has established that this drug is a low ulcerogenic analgesic. The major concerns with paracetamol are the hepatic and renal toxicities which occur infrequently, either from suicide or from accidental poisoning at high doses (Prescott 1992). Accidental poisoning occurs infrequently in children (Penna & Buchanan 1991; Campbell & Oates 1992; Martínez-Mir et al 1996; Webster et al 1996) for whom it is a popular and relatively safe drug and consequently is employed with high frequency (Hawkins & Golding 1995). Reports of hepatotoxicity from paracetamol first arose during the mid-1960s; not long after that it was appreciated that the effect of high toxic doses, such as occur from self poisoning or attempted suicide, can occasionally lead to irreversible liver injury that can be fatal (Prescott 1992). The general assessment is, however, that this is a relatively rare event. The single adult threshold dose of paracetamol which must be taken to produce severe liver damage is 150–250 mg kg^{-1}; this corresponds to plasma concentrations ≥ 200 mg L^{-1} of the drug 4 h after ingestion. Extensive studies have shown conclusively that the mechanism of the irreversible liver damage is related to shunting of the metabolism of paracetamol after reaction with mixed function oxidase (cytochrome P4502E1) to form the metabolite N-acetylbenzoquinoneimine, a highly reactive intermediate. Normally, this metabolite would be conjugated with glutathione and excreted in the urine as mercapturic acid and cysteine conjugates (Prescott 1992). If, however, hepatic concentrations of glutathione are reduced, as they would be from overload of the metabolic pathway or from leakage by aspirin or loss by ethanol, then this can lead to over-production of N-acetylbenzoquinoneimine which has a powerful affinity for proteins in liver cells and initiates a train of events that in experimental animal models can result in irreversible injury and necrosis of hepatocytes (Prescott 1992). Reports of mild or moderate hepatotoxicity from paracetamol (e.g. manifest as hepatitis or elevated plasma levels of liver enzymes) are not, unfortunately, always available to national drug regulatory authorities in the same way as those from NSAIDs, because of the exceptionally large non-prescription use of this drug. Prescription monitoring and other systems would not readily pick

up such incidents with a high degree of accuracy. Hepato-toxicity of paracetamol has been reported in subjects with alcoholic liver disease, and hepatitis and jaundice are occasional features of paracetamol toxicity in young adult patients with measles (Prescott 1992). The question remains whether hepatotoxicity occurs with paracetamol at therapeutic doses, even though it might be extremely rare (Prescott 1992). It is likely that concomitant use of other medications which are known to be hepatotoxic, e.g. potent hepatotoxic NSAIDs such as sulindac, diclofenac and fenbufen (Prescott 1992), could increase the risk of hepatotoxicity otherwise attributed to paracetamol. Indeed, the hepatotoxicity of paracetamol in mice is increased by diclofenac, or vice versa, because diclofenac is converted to an imine metabolite similar to N-acetyl-benzoquinoneimine (Brune & Lindner 1992). The effects of diclofenac in causing liver toxicity might, therefore, have an analogous basis to those of paracetamol.

Acute renal failure is a complication of acute paracetamol poisoning and is often associated with severe liver damage (Prescott 1992). Although the overall incidence is low, renal failure is an important complication in patients with liver damage from paracetamol poisoning. Analgesic nephropathy, which is an important complication of the 'analgesic abuse' syndrome, has been associated with paracetamol but its overall importance has been questioned in the population at large (Prescott 1992). There are indications that analgesic nephropathy is enhanced when paracetamol is taken in combination with NSAIDs (Kleinknecht et al 1986; Prescott 1992). Recent population studies (Steineck et al 1995) suggest that paracetamol might be associated with transitional cell carcinoma. The question of carcinogenicity has been reviewed extensively by Prescott (1992) and the intrinsic risk must be relatively low although these recent epidemiological studies (Steineck et al 1995) give cause for some concern.

Cardiomyopathy can be associated with paracetamol overdose but is certainly not associated with therapeutic doses (Prescott 1992). Additionally, bradycardia, pericardial rub and endocarditis as well as myocarditis, have been associated with paracetamol at toxic doses when in combination with dextropropoxyphene (Prescott 1992). Electrocardiographic abnormalities have been observed in patients with paracetamol poisoning, and hepatic failure has been recorded in these subjects (Prescott 1992). The overall conclusion of Prescott (1992) is that paracetamol is not cardiotoxic by itself but that myocardial damage and cardiac arrhythmias occasionally occur in association with multi-organ failure in patients, from toxic doses of the drug, from other causes. Recent studies have again raised the question about whether paracetamol toxicity can lead to damage of the heart (Brent 1996; Smilkstein 1996). The case reports which have recently highlighted this have usually been of patients who have exhibited hepatotoxicity from intake of toxic quantities of the drug. The strength of association of paracetamol ingestion with cardiac damage has been the subject of detailed analysis (Brent 1996). In applying the criteria for epidemiological evidence of the association of a drug with toxicity, as proposed by the criteria of Sir Austin Bradford-Hill, the analysis suggests the evidence is presently inconclusive (Brent 1996).

The most frequent of the gastrointestinal complications associated with paracetamol (proctitis, rectal ulceration and stenosis) are probably related to the use of suppositories of the drug, most likely in combination with NSAIDs (Prescott 1992). These side-effects are the most direct evidence of gastrointestinal complications from ingestion of paracetamol.

Acute and sub-acute studies of gastrointestinal ulceration and haemorrhage have shown that in comparison with placebo paracetamol does not cause any significant blood loss or endoscopic evidence of damage at therapeutic doses under controlled conditions (Ivey & Settree 1976; Ivey et al 1978; Prescott 1992). These studies are generally supported by experimental studies in laboratory animal models (Prescott 1992). There is, however, some variability in the responses in gastrotoxicity studies in laboratory animal models (Prescott 1992). Thus, the gastric toxicity of ibuprofen has been shown to be potentiated by paracetamol in the rat (Bhattacharya et al 1991), but this has not been confirmed in gastroscopic studies in volunteers (Lanza et al 1986). It might be advantageous to combine these two drugs as there is evidence that centrally mediated analgesia occurs with paracetamol (Urquhart 1994) possibly in a manner different from that of NSAIDs (Rainsford 1996a, b). In some studies paracetamol has been shown to protect against gastric mucosal injury from NSAIDs and ethanol (Prescott 1992).

A variety of Type-B reactions is associated with paracetamol intake; these include allergy, anaphylaxis, urticarial reactions, asthma and bronchospasm, as well as dermatological reactions, principally rash and various eruptions (Prescott 1992). These skin reactions are amongst the commonest of such reactions and could possibly be regarded as Type A. Fatalities as a result of Stevens-Johnson syndrome and other severe maculopapular and erythematous conditions have, furthermore, been reported in a few patients who have consumed paracetamol, in some cases in combination with other drugs (Prescott 1992).

Apart from its use in patients with rheumatic disorder as a supplementary or rescue analgesic, paracetamol has been advocated for use as a first-line analgesic in patients with osteoarthritis (Jones & Doherty 1992) in the belief it might be less likely to accelerate joint damage as observed with indo-methacin and other potent prostaglandin-synthesis-inhibitory NSAIDs (Rashad et al 1989, 1992; Rainsford 1996a, b). Balanced against this view is the finding that paracetamol gives lower pain relief in this condition than NSAIDs (March et al 1994). In experimental pain in human volunteers paracetamol has no effect against hyperalgesia whereas therapeutic doses of ibuprofen are hypoalgesic (Forster et al 1992).

The high doses of paracetamol (≥ 4 g) ingested long-term for analgesia in osteoarthritis have not been reported to be associated with reports of hepatotoxicity (Prescott 1992). This possibility must, however, be a concern with this drug because there do not appear to have been long-term studies of ingestion of the drug at very high doses in which this aspect has been specifically examined.

Adverse reactions and toxicology of ibuprofen

The overall incidence and severity of adverse events associated with ibuprofen is low in comparison with other NSAIDs (Royer et al 1984; Bird 1985; Veltri & Rollins 1988; Paulus 1990). In a review in 1990, seven years after the introduction of ibuprofen OTC, the US Food and Drug Administration Arthritis Advisory Committee considered, in detail, the use of

NSAIDs and analgesics for OTC self-medication. They were particularly concerned that a number of NSAIDs that have been prescribed extensively for more than 10 years might be potential candidates for non-prescription use.

In a submission to the FDA Arthritis Advisory Committee, the American College of Rheumatology stated that at the recommended doses (200–400 mg every 4–6 h with a maximum daily dose of 1200 mg) ibuprofen did not appear to be associated with any serious renal, hepato- or gastro-toxicity problems. The College was not aware of any evidence of spontaneous ingestion of high anti-inflammatory doses of 2400–3600 mg daily during self-medication of OTC forms without prescription, possibly because this would require taking 12–18 of the relatively expensive 200-mg tablets daily. This implied that cost to the patient might have a moderating influence on the misuse or abuse of this drug. They considered ibuprofen overdose less likely to result in hospitalization than aspirin or paracetamol overdoses, and deaths as a result of overdose of ibuprofen alone have been exceedingly rare. The College also concluded that the relative safety of ibuprofen is particularly impressive especially when compared with that of aspirin. The lack of long-lasting anti-coagulant activity and appreciably low incidence of peptic ulcers with ibuprofen were considered particularly advantageous in comparison with aspirin. The submission also noted that the prominent use of the generic name, ibuprofen, on all advertising and packaging materials gave clear and unconfusing messages to the public, whereas the multiple brand names of aspirin of varying strength creates conditions for potential misuse or inappropriate use, or lack of knowledge by the public of the contents of the drug, or both. The FDA Arthritis Advisory Committee had, on the basis of its experience with ibuprofen, suggested that for any other drugs to be approved for non-prescription use safety should be the paramount consideration, because efficacy is assumed. This basis has indeed been the major reason for the success of ibuprofen (Paulus 1990). In a supplementary note Paulus (1990) also stated that it would be questionable whether aspirin should not in fact be made a prescription-only drug because its side-effects are unacceptably high. These and other comments to the Arthritis Advisory Committee have provided interesting insight into the safety of ibuprofen in comparison with that of aspirin under OTC conditions.

At anti-rheumatic doses the toxicity of ibuprofen in man ranks amongst the lowest, if not the lowest, of all NSAIDs (Pavelka et al 1978; Brune 1986; Levy 1987; Weber 1987; Wiholm et al 1987; Veltri & Rollins 1988; Fries et al 1991; Carson & Strom 1992; Rainsford & Quadir 1995) even when adjusted for defined daily dosages (Wiholm et al 1987).

The principal Type-A adverse events recorded in association with ibuprofen administered at anti-rheumatic doses are: potentially life-threatening events, those affecting the gastrointestinal tract (e.g. haematemesis, malaena, peptic ulcer, severe gastric pain or vomiting) being of low incidence (approximately 1.5% compared with placebo 1% and 12.5% for aspirin); symptomatic adverse effects comprising non-specific rash, occasionally headache, depression and somnolence, which are extremely rare; hypersensitivity reactions which occur infrequently (e.g. bronchospasm and asthma, the incidence of which is low and probably about equal with that of paracetamol (Settipane 1983)); and interference with clin-

ical pathology tests, and these are few (e.g. Bishnoi et al 1994). Among the last are reports of ibuprofen therapy in patients with rheumatic disorders resulting in reduced albumin, uric acid and creatinine (Jelic-Ivanovic et al 1985) whereas short-term inhibition of platelet aggregation is the only laboratory assessment shown to be affected by the drug in normal volunteers (Royer et al 1985; Dollery 1991).

Renal side-effects reflecting change in blood-urea nitrogen or elevated serum creatinine occur in approximately 1% of patients with rheumatic disorders (Bonney et al 1986). Acute renal insufficiency, a rare condition associated with ingestion of large quantities of ibuprofen ($ > 400$ mg kg^{-1}) in adults and children, is reversible (Kim et al 1995). In normal subjects, ibuprofen, like paracetamol, does not produce enzymuria as observed with aspirin (Proctor & Kunin 1978).

Under OTC conditions, in patients with rheumatoid arthritis or osteoarthritis, it has been claimed that tests have shown the hepatic safety of ibuprofen to be better than that of aspirin, with no observed elevation of AST levels compared with an incidence of about 5% with aspirin (Freeland et al 1988). In an analysis of 1100 cases of drug-induced hepatic injury reported to the Danish Committee on Adverse Reactions during 1978–87, only 17 cases were attributed to ibuprofen; two of these were fatal (Friis & Andreasen 1992). These contrasted with appreciably more severe hepatotoxicity attributed to sulindac and sulphasalazine, and with acute cytototoxic effects from paracetamol in non-alcoholic subjects (Friis & Andreasen 1992). The low hepatotoxicity of ibuprofen in comparison with paracetamol is reflected in reports to the American Association of Poison Control Centers (Veltri & Rollins 1988); it probably reflects the lack of formation on reactive metabolites (c.f. paracetamol) during the extensive liver metabolism ($ < 90\%$) of the drug (Dollery 1991). The two principal metabolites of ibuprofen, formed by cytochrome oxidation (Fracasso et al 1992) presumably by cytochrome P4502C isotype, are the hydroxyl and carboxyl derivatives (2-[4-(1-hydroxy-2-methylpropyl)phenyl]propionic acid and 2-[4-(carboxypropyl)phenyl]propionic acid, respectively) (Adams et al 1970; Dollery 1991; Rudy et al 1991). Subsequent conjugation of the parent drug and these two metabolites with glucuronic acid also occurs (Rudy et al 1991); the hydroxyl, carboxyl and glucuronic acid derivatives are all pharmacologically inactive (Dollery 1991). The taurine conjugate of ibuprofen which occurs via formation of ibuprofenyl coenzyme A thioester is a minor metabolite only; 1.5% is formed after ingestion of 400 mg ibuprofen (Shirley et al 1994). The extensive liver microsomal metabolism of ibuprofen does not result in impaired aminopyrine clearance (Abernethy & Greenblatt 1983).

Under controlled trial conditions in German-speaking countries the SPALA (Safety Profile of Anti-rheumatics in Long Term Administration) Group monitoring NSAIDs reported that the incidence of adverse events for prescription dosage ibuprofen was 11.2% in the gastrointestinal system, 3.3% in skin and appendages, 3% in liver and peripheral and nervous systems, 0.7% in liver and biliary system, with the body as a whole having an incidence of 2.2% (Brune et al 1992). The frequency of these adverse events with ibuprofen was lower than that with indomethacin, acemetacin and diclofenac, all of which, like ibuprofen, were among the most frequently prescribed of all NSAIDs (Brune et al 1992).

Reviews of published trials of ibuprofen compared with other NSAIDs in the therapy of osteoarthritis have consistently shown lower frequencies of adverse effects with ibuprofen, although some variability is noted with therapeutic response to low doses of this drug (Altman 1984). This low frequency of adverse effects might, in fact, relate to pattern of use in treating rheumatic conditions (Luggen et al 1989) because ibuprofen tends to be prescribed more at low doses in the early stage of these diseases (Davis et al 1995). There is, therefore, a perception that this drug is less effective than more potent NSAIDs, although it is equipotent with other NSAIDs in paediatric rheumatic diseases (Hollingworth 1993). Stereoselective metabolism of ibuprofen occurs in man; the prostaglandin synthesis inactive form, $R(-)$, is approximately 30–60% metabolized to the prostaglandin synthesis active form, the $S(+)$ enantiomer (Williams & Day 1985; Caldwell & Hutt 1987; Rudy et al 1991; Geisslinger et al 1993) and this has been claimed to account for some variability in response to the drug (Williams & Day 1985; Geisslinger et al 1993). The intrasubject variability in therapeutic response to ibuprofen is, however, relatively low (Wagner & Vögtle-Junkert 1996). Whether appreciable population variability accounts for the susceptibility to side-effects has not been established, although the indications are that the variability of the bioconversion of the $R(-)$ form to the $S(+)$ form, with consequent changes in the metabolism of the drug, might not be very pronounced (Rudy et al 1991; Geisslinger et al 1993). Indeed, the greatest source of variability probably arises from the different doses and formulations of racemic ibuprofen currently available (Saano et al 1991; Jamali et al 1992; Theis et al 1994). These pharmacokinetic features of ibuprofen are relevant to the safety (and efficacy) of the drug.

The pharmacokinetics of ibuprofen are not markedly influenced by age (Albert & Gernaat 1984; Albert et al 1984; Dollery 1991), even in children (Nahata et al 1991), in patients with renal insufficiency (Ochs et al 1985; Dollery 1991), by the febrile state in children (Nahata et al 1991), or in patients with rheumatoid arthritis (Albert & Gernaat 1984). Differences have, however, been observed in the stereoselective metabolism or elimination of the enantiomers of ibuprofen in patients with pre-existent renal failure after a single dose of 800 mg racemic ibuprofen (Chen & Chen 1994). Metabolism of $R(-)$ to $S(+)$ ibuprofen is accelerated in these subjects and, with reduced renal elimination of the enantiomers, leads to elevated plasma levels of the $S(+)$ form which could promote toxic effects of this drug (Chen & Chen 1994). It has been claimed that ibuprofen pharmacokinetics are not affected in subjects with alcoholic liver disease (Albert & Gernaat 1984), although other studies show that $R(-)$ to $S(+)$ conversion is slowed and elimination prolonged in subjects with cirrhosis. These differences might be related to the severity of liver pathology; the more severe cirrhotic state resulting in more pronounced effects. Overall, the studies reported would appear to indicate that in pharmacokinetic terms, ibuprofen has a relatively wide safety margin in conditions where liver or renal metabolism might be compromised, or in inflammatory diseases.

The metabolic conversion of $R(-)$ ibuprofen to its $S(+)$ enantiomer which occurs in liver, intestine and adipose tissue (Williams & Day 1985; Williams et al 1986; Jeffrey et al 1991; Menzel-Soglowek et al 1993; Shirley et al 1994; Tracy et al 1993) proceeds by an acyl-coenzyme-A intermediate which

can itself lead to the formation of triglyceride derivatives, because this involves part of the normal metabolic route of triglyceride formation and metabolism. Although there has been interest in the biochemistry of this reaction, the suggested relationship to liver or other toxicities (Boelsterli et al 1995) has not been established. Although ibuprofen, like other NSAIDs, has been shown to inhibit mitochondrial β-oxidation of palmitate by a non-stereoselective mechanism (Zhao et al 1992), the postulated consequence of this for the development of microvesicular steatosis does not appear to have been reported with ibuprofen (Boelsterli et al 1995).

Clinically significant drug interactions which might occur as a result of pharmacokinetic alterations by ibuprofen or because of the actions of other drugs on ibuprofen appear to be limited to this drug displacing phenytoin from albumin (Bachmann et al 1986; Johnson et al 1994) or to the concurrent intake of magnesium hydroxide enhancing oral absorption of ibuprofen (Neuvonen 1991). The plasma levels of digoxin are not altered by ibuprofen (600 mg three times a day) although they are increased by indomethacin (Jørgensen et al 1991). No effect of ibuprofen on blood pressure-lowering effects of hydrochlorothiazide or enalapril have been observed although plasma renin activity was reduced with ibuprofen (Koopmans et al 1987) and blood pressure and other parameters of cardiovascular function are not affected by ibuprofen in normal or hypertensive subjects (Camu et al 1992) or in diabetic patients (Bakris et al 1995). Frusemide-induced diuresis, but not naturesis, has been found to be inhibited by ibuprofen (400 mg and 800 mg) in normal subjects (Passmore et al 1990). Naturesis is unaffected by ibuprofen (800 mg) in diabetic patients although glomerular filtration is reduced (Bakris et al 1995). No significant effects of ibuprofen (1200 mg three times a day) were observed on the control of fasting blood sugar with chlorpropamide (Shah et al 1984). These results suggest that pharmacokinetic or pharmacodynamic alterations consequent upon drug interaction with ibuprofen are relatively few and well defined in certain states or conditions.

Studies with laboratory animals suggest that the principal toxicological effects of ibuprofen at high dose are confined to the gastrointestinal tract (Adams et al 1969; Whitehouse & Rainsford 1987; Dollery 1991). In comparison with other NSAIDs, studies in animal model systems show that ibuprofen is of low to moderate mucosal ulcerogenicity in the gastrointestinal tract; the principal effects of the drug are confined to the stomach where it produces mucosal irritation (Adams et al 1969; Whitehouse & Rainsford 1987; Wiseman & Noguchi 1987). It is significant that no appreciable intestinal damage has been reported except at very high doses for long periods (Adams et al 1969). This is a very important issue in view of current concerns that some NSAIDs, e.g. diclofenac and indomethacin, might cause intestinal perforation, diaphragmlike strictures and adhesions in patients with rheumatic disorders (Bjarnason 1988; Rainsford 1994; Rainsford & Quadir 1995). There are no appreciable differences between the $R(-)$ and the $S(+)$ form in producing mucosal injury in the stomach of mice; the lack of any difference might be related to intrinsic low ulcerogenicity of the drug combined with metabolic inversion in this species (Rainsford 1995). The low incidence of gastric mucosal damage from racemic ibuprofen would seem to be unrelated to the selective inhibition of cyclooxygenase-2 compared with cyclooxygenase-1, because racemic

ibuprofen is approximately equipotent as an inhibitor of cyclooxygenase-1 and -2 (O'Neill et al 1993; Laneuville et al 1994; Smith et al 1994; Vane & Botting 1995). The low ulcerogenic activity of ibuprofen is, therefore, most probably a consequence of the prodrug-like character of the $R(-)$ enantiomer present in half the mass of the racemate, and of the other pharmacokinetic features of the drug. As noted above, paracetamol might enhance the ulcerogenicity of ibuprofen (Bhattacharya et al 1991) but this has not been shown in endoscopic studies in volunteers (Lanza et al 1986). The visual disturbances occasionally reported with NSAIDs also occur with ibuprofen; visual fields, acuity and colour sensitivity are unaffected although transient reduction in contrast sensitivity is observed (Ridder & Tomlinson 1992).

Type-B adverse reactions have been infrequently or occasionally reported; they include eosinophilic meningitis in a young woman (Quinn et al 1984); ibuprofen has also been shown to induce meningitis in the NZB × NZW mouse (Berliner et al 1985). Other reports include: haemolytic anaemia (the relationship to glucose-6-phosphate dehydrogenase deficiency being undefined, Sanford-Driscoll & Knodel 1986); acute encephalopathy in two patients with connective tissue disease (Agus et al 1990); acute thrombocytopenia from an antibody-mediated mechanism in a patient with ankylosing spondylitis (Meyer et al 1993); ulcerative proctitis in a girl with juvenile systemic lupus erythematosus (Khoury 1989); mild constriction of the ductus arteriosus and reversible oligouria (Østensen 1994); and one case of thrombocytopenia (Jain 1994).

Among the possible beneficial side-effects of ibuprofen are: the inhibition of glucose-modification of eye lens proteins, which might be an indication of benefit of the drug against cataract formation (Raza & Harding 1991); the inhibition of alcohol-induced teratogenic activity (Randall et al 1991) and behavioural/cognitive effects (Naranjo & Bremner 1993); relief of muscle soreness in exercise (Hasson et al 1993); protection against brain trauma (Hall 1985); protection against myocardial damage (Evans et al 1985); and, as with other NSAIDs, possible reduction in Alzheimer's and related dementias (Rainsford 1996a) and breast cancer (Harris et al 1996). The clinical proof of many of these claims has not yet been established.

This review indicates that the overall toxicity of ibuprofen is relatively low compared with that of other NSAIDs and analgesics. The drug does not have the hepato-renal toxicity evident with paracetamol. Although the risks of gastro-intestinal ulceration and bleeding are low (Rainsford & Quadir 1995) they are probably slightly greater than those of paracetamol. Thus, the particular interest in terms of the predominant Type-A adverse events in the subsequent analysis of OTC events will be an examination of the potential of ibuprofen to cause gastrointestinal adverse events in comparison with that of paracetamol. The following examination of clinical trials which have been reported with these two drugs taken OTC will address the gastrointestinal adverse events in particular. These would be expected to be of higher frequency than other side-effects including those in the skin, central nervous system and hepato-renal systems, which have been analysed above in subjects with rheumatic disorders (Brune et al 1992).

Adverse Reactions to OTC Drug Doses

Databases for the analyses

The literature used for the analyses was derived from Medline on-line retrieval, and from manual searches dating back to the introduction of ibuprofen in 1969, and of paracetamol in the mid-1960s. Additional databases searched include BIDS and Excerpta Medica. It emerged that the most relevant papers were those published after 1981 because they met criteria essential for the selection of data for these analyses.

The inclusion criteria were: prospective controlled or uncontrolled (with respect to placebo), blinded or unblinded studies in which either ibuprofen or paracetamol were treatments of primary interest; single or multiple daily dosing orally (or in a few cases rectally) taken at recommended OTC dosages; and adverse events should have been monitored.

Exclusion criteria were: use of one of these drugs for rescue analgesia; perioperative use where there was a risk that previous or concurrent operative medications could have interfered with the actions of the drugs under analysis; paracetamol used as a marker of gastric emptying or where adverse events were not specifically recorded or monitored; and use of combined medications.

OTC dosages

Maximum single or daily doses of paracetamol were: adults, 1 g single dose, 4 g daily; children <3 months, 5 or 10 mg kg^{-1} or 60 mg single dose, 120 mg daily; children 3 months to 1 year, 120 mg single dose, 480 mg daily; children 1–5 years, 250 mg single dose, 1 g daily; and children 6–12 years, 500 mg single dose, 2 g daily.

Maximum single or daily doses of ibuprofen were: adults, 400 mg single dose, 1200 mg daily; children 1–12 years divided doses, 20 mg kg^{-1}; or children 1–2 years, 50 mg single dose, 200 mg daily; children 3–7 years, 100 mg single dose, 400 mg daily; children 8–12 years, 200 mg single dose, 800 mg daily.

We have included data from a substantial number of reports that have reported drug dosages which have exceeded the normal recommended period of time for self-administered OTC dosage for the drugs. In the case of ibuprofen this is generally a maximum of seven days; the exact limited period for paracetamol is less clear. Thus, we have later segregated the data to include only those where the recommended time period, i.e. less than seven days, was followed. With these data we have undertaken analysis of variance in those studies where treatment was of ≥ 40 subjects to establish if there are differences in the percentage of individual adverse events in each major organ system as well as in the total number of adverse events.

The literature search revealed 730 potentially useful publications, of which 111 fulfilled the essential criteria. Of these 111, three were open-labelled, in four the level of blinding was not specified, and eight were only single-blind, i.e. a total of 96 trials were randomized and double blinded. The other data were included because they add meaningfully to the data base without unduly affecting the statistical analyses.

For the purposes of definition, children are regarded as being under 18, the elderly 60 years or older. The description of the organ system in which the adverse events are recorded is according to the standard Costart dictionary terms. The adverse

events that have been recorded are in the form of the number and percentage of single events identified in patients.

Overall safety of ibuprofen and paracetamol

Table 1 shows the distribution of data on adverse events recorded in all the trials where ibuprofen or paracetamol were included. These data do not always represent direct comparisons of ibuprofen with paracetamol, the data for these being shown in Table 2. It should first be noted that the total number of patients exposed to paracetamol was nearly double that for ibuprofen (Table 1) — a total of 5958 patients received paracetamol and 3111 received ibuprofen. Any statistical analysis or quantitative assessment must bear in mind that these denominator values are different (i.e. for calculations of the proportion of subjects with adverse events in relation to the total number of study subjects). It is well known that denominator variations can markedly influence the statistics of adverse events (Weber 1984). Given this proviso it would appear that the total overall percentage of patients having adverse events is 10% with paracetamol compared with 8% with ibuprofen. The percentage of overall adverse events does not appear to vary appreciably for drug exposure up to 30 days. There is, however, a marked difference between the percentage of adverse events with ibuprofen where the drug is being given for 31–90 days (29%) compared with the 8–30 day period (19%). Unfortunately, there are no comparable data available in the 31–90 day period for paracetamol. The increase in incidence of adverse events in the 1–3 month period is not unexpected, because it is known that adverse event rates increase with time of drug exposure (Weber 1984, 1987).

Where ibuprofen and paracetamol were compared in the same trial (Table 2), there are five trials where the incidence of adverse events was greater with paracetamol than with ibuprofen and one where the incidence of adverse events was greater with ibuprofen than with paracetamol. The remainder showed no recorded adverse events in either groups. It should be noted that these data and those discussed above (Table 1) comprise studies in which the number of subjects per group is often quite small. It should be noted that the trials including both paracetamol and ibuprofen were all for patients which had received the drug for ≤ 28 days.

Gastrointestinal adverse events, which tend to make up the majority of adverse events, were usually cases of dyspepsia, nausea or vomiting. None of the gastrointestinal events

appeared to have been followed up with investigations (endoscopy, barium meal), implying that there were no cases of severe gastrointestinal ulceration or haemorrhage. None of the papers referred to any serious adverse events having occurred (Table 3).

Demographic Distribution

A total of 10 studies featured adverse-event records in children and five in elderly subjects (≥ 60 years of age) (Table 4). The only striking feature of these data is the higher rate of adverse events in children under the age of 4 years. Several of these adverse events were febrile seizures, which the drugs were being taken to prevent. The adverse event rate was slightly higher in the paracetamol groups (22%) than in the ibuprofen group (18%). No differences were observed between adverse events in males and females, irrespective of age (data not shown).

Details of adverse events

The details of the selected studies are shown in Table 3. Some of the studies did not record particular categories of known adverse events in some of the major organ systems even though total values were given. It is also important to note that although the majority of reports might have noted a negative result for a particular category of adverse event there were some studies where no statement was made so we have not assumed this to have a null event. When the data on all the adverse events are considered there are no apparent differences from inspection of the reports in the subjects that received ibuprofen compared with those that had paracetamol (Table 3).

Although we recognize that the above mentioned data are very selective and are based on information derived from a variety of trial designs and populations, it is nonetheless instructive for indicating a relatively low incidence of severe adverse reactions with both drugs when taken at their respective OTC dosages.

Data from studies with group sizes > 40 subjects and with < 7 days' treatment

In a detailed breakdown of the published studies into study designs and treatments, specific adverse events in organ systems, and principal study outcomes from ibuprofen (Table 5)

Table 1. Overall adverse event rates and exposure grouped by duration of dosing.

Days dosed	Drug	Number of groups	Exposure*	Total number of patients	Overall percent with adverse events	Total number with adverse events†	Total number of adverse events‡
< 1	Paracetamol	27	0	4644	10	444	479
< 1	Ibuprofen	25	0	2312	6	148	172
1	Paracetamol	11	420	420	10	43	49
1	Ibuprofen	5	215	215	8	18	22
2–7	Paracetamol	15	2882	687	8	57	64
2–7	Ibuprofen	9	1015	227	9	20	29
8–30	Paracetamol	6	5496	207	19	39	39
8–30	Ibuprofen	9	5960	272	19	52	52
31–90	Ibuprofen	5	6504	85	29	25	29
Total	Paracetamol	59	8798	5958	10	583	631
Total	Ibuprofen	53	13694	3111	8	263	304

*Number of patient days. †Adverse events grouped as the total number of patients having these events. ‡Adverse events grouped as the total of all recorded adverse events. Full details of the data reported in this table can be obtained from K. D. Rainsford.

Table 2. Adverse events in trials where ibuprofen and paracetamol were compared.

Days dosed	Drug	Percent with adverse events	Number with adverse events*	No. of patients	Total exposure†	Number of adverse events‡	Reference
< 1	Ibuprofen	2	21	878	0	3	Furey et al (1992)
< 1	Paracetamol	3	27	849	0	31	Furey et al (1992)
< 1	Ibuprofen	0	0	39	0	0	Schachtel & Thoden (1993)
< 1	Paracetamol	0	0	38	0	0	Schachtel & Thoden (1993)
< 1	Ibuprofen	9	27	306	0	27	Mehlisch et al (1990)
< 1	Paracetamol	10	32	306	0	33	Mehlisch et al (1990)
< 1	Ibuprofen	0	0	36	0	0	Schachtel et al (1989)
< 1	Paracetamol	0	0	37	0	0	Schachtel et al (1989)
< 1	Ibuprofen	8	5	61	0	6	Cooper et al (1989)
< 1	Paracetamol	19	11	59	0	13	Cooper et al (1989)
< 1	Ibuprofen	0	0	20	0	0	Kauffman et al (1992)
< 1	Paracetamol	0	0	8	0	0	Kauffman et al (1992)
< 1	Ibuprofen	0	0	39	0	0	Schachtel et al (1988)
< 1	Paracetamol	0	0	40	0	0	Schachtel et al (1988)
< 1	Ibuprofen	0	0	14	0	0	Moore et al (1985)
< 1	Paracetamol	0	0	11	0	0	Moore et al (1985)
1	Ibuprofen	18	6	34	34	6	Van Esch et al (1995)
1	Paracetamol	22	8	36	36	8	Van Esch et al (1995)
7	Ibuprofen	0	0	8	56	0	Furey et al (1993)
7	Paracetamol	0	0	8	56	0	Furey et al (1993)
21	Ibuprofen	33	4	12	252	4	Radack et al (1987)
21	Paracetamol	20	3	15	315	3	Radack et al (1987)
28	Ibuprofen	26	16	62	1736	16	Bradley et al (1991)
28	Paracetamol	31	19	61	1708	19	Bradley et al (1991)

*Adverse events grouped as total number of patients having these events. †Number of patient days. ‡Adverse events grouped as the total of all recorded adverse events. Full details of the data reported in this table can be obtained from K. D. Rainsford.

and from paracetamol (Table 6) it can be seen from inspection of the data and from analysis of variance (Tables 7 and 8) that there are no differences in the overall and individual adverse events recorded in those studies where the drug was taken for ≤ 7 days. Neither were there any overall differences in adverse events when more than 40 subjects received one of the drugs (denoted '§§' in Tables 5 and 6). We took an arbitrary level of ≥ 40 subjects because subjectively it appeared that this was a reasonable balance between achieving a reasonable number of study subjects for comparison bearing in mind that the number of subjects in many of the trials is relatively low.

The analysis of variance of data for adverse events reported in the major organ systems in the studies where the studies were performed in more than 40 subjects is shown in Table 8, in which ibuprofen and paracetamol are directly compared. These data showed that again there were no statistically significant differences ($P > 0.05$, analysis of variance, F-test) in the adverse events recorded between the two drug treatments (Table 8).

There were no differences in the reports of adverse events when these were considered again within organ systems (e.g. nausea, vomiting, in the gastrointestinal systems). There were no statistically significant differences between the results with the two drugs (Tables 7 and 8). In one study gastrointestinal blood loss was determined in response to ibuprofen treatment (Bidlingmaier et al 1995). A statistically significant increase in mean blood loss of $+0.52$ mL day^{-1} occurred with ibuprofen compared with the pre-treatment baseline period ($+0.38$ mL day^{-1}) in six subjects who took 400 mg ibuprofen three times a day orally for 5 days (Bidlingmaier et al 1995). The mean blood loss observed was appreciably less than that which occurred with 500 mg aspirin three times a day ($+2.02$ mL day^{-1} compared with $+0.35$ mL day^{-1} in the corresponding

pre-treatment placebo period (Bidlingmaier et al 1995). Similar results have been reported in other studies (Warrington et al 1982; Aabakken et al 1989). Although it is known that paracetamol does not cause significant blood loss above that caused by placebo, the average value of this is about $+0.8$ mL day^{-1} (Loebl et al 1977; Johnson & Driscoll 1981; Konturek et al 1984) and this would appear to be within the range of blood loss from ibuprofen ($+0.52$ mL day^{-1}; Bidlingmaier et al 1995). Whereas no direct studies have been performed to compare gastrointestinal blood loss as a result of ibuprofen with that resulting from paracetamol, it is unlikely that there will be any difference between the effects of these two drugs at OTC dosages because of this potential overlap and the relatively low values of blood loss noted in these earlier studies.

As mentioned in the previous section, the adverse events were minor in both treatment groups and there was no evidence of any serious reactions requiring major intervention. In only one study was ibuprofen withdrawn from treatment of one patient. It is clear that the adverse events reported were all within the scope of being manageable by the subjects themselves and would have expected to have been reversible upon cessation of the drug.

Relation to Therapeutic Use and Efficacy

Inspection of the details on types of trials and pain response in Table 5 shows that, overall, paracetamol and ibuprofen have shown similar therapeutic effects especially where there is substantial data in appropriate pain models (e.g. 3rd molar extraction) in a sufficient number of subjects (i.e. ≥ 40; denoted '§§' in Tables 5 and 6). Some studies in which ibuprofen and paracetamol have been directly compared have indicated that ibuprofen is more potent. This might reflect the

Table 3. Adverse events by Costart term.

Days dosed	Indication	Total adverse events	Costart term*	Reference
A. With ibuprofen				
< 1	Pain	23	Rash (1; 4%), paresth. circumoral (1; 4%), neck rigid (1; 4%), headache (5; 22%), dizziness (1; 4%), somnolence (6; 26%), gastrointestinal dis (8; 35%)	Furey et al (1992)
< 1	Dental extractions	12	Vasodilatation (1; 8%), asthenia (1; 8%), somnolence (8; 67%), abnormal thoughts (1; 8%), tinnitus (1; 8%)	Cooper et al (1982)
< 1	Dental extractions	8	Headache (2; 25%), somnolence (1; 13%), nausea (1; 13%), asthenia (1; 13%), agitation (1; 13%), dizziness (1; 13%), nervousness (1; 13%)	Forbes et al (1991b)
< 1	Dental extractions	35	Bleeding (2; 6%), dizziness (2; 6%), dyspepsia (1; 3%), oedema general (2; 6%), fever (3; 9%), headache (6; 17%), nausea (6; 17%), somnolence (10; 29%), vomiting (3; 9%)	Jain et al (1986a)
< 1	Volunteers	4	Mucous membrane dis (4; 100%)	Bergmann et al (1992)
< 1	Oral surgery	27	Dizziness (3; 11%), somnolence (6; 22%), headache (2; 7%), gastrointestinal dis (16, 59%)	Mehlisch et al (1990)
< 1	Volunteers	4	Asthenia (2; 50%), headache (2; 50%)	Karttunen et al (1990)
< 1	Dental extractions	1	Asthenia (1; 100%)	Ahlstrom et al (1993)
< 1	Dental extractions	6	Headache (2; 33%), somnolence (4; 67%),	Cooper et al (1989)
< 1	Dental extractions	27	Nervousness (3; 11%), dizziness (1; 4%), vomiting (3; 11%), tinnitus (1; 4%), somnolence (6; 22%), ear pain (1; 4%), nausea (1; 4%), insomnia (1; 4%), fainting (1; 4%), asthenia (1; 4%), agitation (1; 4%), headache (7; 26%)	Forbes et al (1991a)
< 1	Dental extractions	8	Dizziness (2; 25%), somnolence (1; 13%), abdominal pain (1; 13%), headache (1; 13%), asthenia (1; 13%), amblyopia (1; 13%), nervousness (1; 13%)	Forbes et al (1992)
< 1	Dental extractions	11	Anxiety (1; 9%), nausea (1; 9%), somnolence (5; 45%), vasodilation (1; 9%), vomiting (1; 9%), dizziness (1; 9%), headaches (1; 9%)	Hersh et al (1993)
1	Fever	1	Rash (1; 100%)	Marriott et al (1991)
1	Febrile seizures	6	Hypothermia ((2; 33%), insomnia (1; 17%), rash (1; 17%), convulsions (2; 33%)	Van Esch et al (1995)
1	Coxarthrosis	8	Nausea (3, 38%)	Quiding et al (1992)
1	Dental extractions	7	Asthenia (1; 14%), sweat (1; 14%), nausea (3; 43%), headache (1; 14%), hypotens. pos.(1; 14%)	Petersen et al (1993)
2	Foot surgery	7	Headache (1; 14%), nausea (1; 14%), pruritus (1; 14%), tinnitus (2; 29%), urticaria (1; 14%), constipation (1; 14%)	Wittenberg et al (1984)
3	Dental extractions	4	Nausea (1; 25%), somnolence (1; 25%), dizziness (1; 25%), headache (1; 25%)	McQuay et al (1989)
6	Dental extractions	13	Bleeding (2; 15%), headache (3; 23%), nausea (3; 23%), somnolence (3; 23%), sweating (1; 8%); vomiting (1; 8%),	McQuay et al (1993)
7	Sports injuries	1	Gastroenteritis (1; 100%)	Walker et al (1984)
7	Volunteers	4	Dyspepsia (1; 25%), nausea (1; 25%), abdominal pain (2; 50%)	Puscas et al (1989)
14	Rheumatoid arthritis	1	Nausea, vomiting (1; 100%)	Hill et al (1990)
14	Osteoarthritis	16	Rash (1; 6%), abnormal dreams (1; 6%)	Lambert et al (1985)
21	Hypertension	4	Somnolence (1; 25%), flatulence (1; 25%), pruritus (1; 25%), rash (1; 25%)	Radack et al (1987)
28	Osteoarthritis	16	Nervous system (7; 44%), oedema general (2; 13%), gastrointestinal dis (5; 31%)	Bradley et al (1991)
28	Osteoarthritis	3	Dyspepsia (1; 33%), somnolence (2; 67%)	Vlok & Van Vuren (1987)
30	Osteoarthritis	8	Gastrointestinal dis (7; 88%), rash (1; 13%)	Di Perri et al (1987)
40	Menstrual bleeding	11	Nausea (2; 18%), headache (2; 18%), dyspepsia (1; 9%), diarrhoea (1; 9%), dizziness (1; 9%)	Makarainen & Ylikorkala (1986)
56	Rheumatoid arthritis	3	Abdominal pain (3; 100%)	Alam & Kabir (1983)
60	Osteoarthritis	9	Sweat (1; 11%), rash (1; 11%), abdominal pain (3; 33%), nausea (1; 11%), dyspepsia (3; 33%)	Kaik et al (1991)

Table 3.   *(continued)*

Days dosed	Indication	Total adverse events	Costart term*	Reference
84	Osteoarthritis	5	Urea clearance decrease (1; 20%), creatinine increase (1; 20%), hypertension (1; 20%), phosphatase alk. (1; 20%), rash (1; 20%)	Admani & Verma (1983)
90	Non-articular rheumatism	12	Dyspepsia (7; 58%), flatulence (1; 8%), nausea (2; 17%), abdominal pain (1; 8%), constipation (1; 8%)	Valle-Jones et al (1984)
B. With paracetamol				
< 1	Strabismus surgery	2	Nausea, vomiting (2; 100%)	Morrison & Repka (1994)
< 1	Dental extractions	3	Headache (1; 33%), nausea (1; 33%), somnolence (1; 33%)	Forbes et al (1989)
< 1	Acute Pain	31	Diarrhoea (1; 3%), somnolence (13; 42%), eye pain (1; 3%), nervousness (1; 3%), headache (1; 3%), dizziness (4; 13%), ataxia (1; 3%), anxiety (1; 3%), gastrointestinal dis (8; 26%)	Furey et al (1992)
< 1	Episiotomy	6	Dizziness (3; 50%), somnolence (3; 50%)	Rubin & Winter (1984)
< 1	Dental extractions	2	Pain (1; 50%), headache (1; 50%),	Forbes et al (1984a)
< 1	General surgery	15	Sweat (3; 20%), somnolence (5; 33%), vomiting (1; 7%), abdominal pain (2; 13%), nausea (3; 20%), pharyngitis (1; 7%)	Gertzbein et al (1986)
< 1	Headache	13	Gastroenteritis (7; 54%)	Peters et al (1983)
< 1	Dental extractions	9	Nausea, vomiting (2; 22%), somnolence (4; 44%), headache (1; 11%)	Dionne et al (1994)
< 1	Muscle contraction headache	5	Nausea (1; 20%), somnolence (1; 20%), insomnia (1; 20%), dry mouth (1; 20%), diarrhoea (1; 20%)	Miller et al (1987)
< 1	Oral surgery	33	Dizziness (6; 18%), gastrointestinal dis (13; 39%), headache (4; 12%), somnolence (10; 30%)	Mehlisch et al (1990)
< 1	Dental extractions	13	Nausea (2; 15%), nervousness (1; 8%), dizziness (2; 15%), somnolence (8; 62%)	Cooper et al (1989)
< 1	Episiotomy or dental surgery	27	Dizziness (6; 22%), gastrointestinal dis (2; 7%), somnolence (19; 70%)	McMahon et al (1987)
< 1	Oral surgery	31	Nausea (7; 23%), vomiting (6; 19%), vertigo (1; 3%), appetite change (1; 3%), somnolence (5; 16%), hypotens pos. (1; 3%), headache (1; 3%), hallucinations (1; 3%), gastroenteritis (1; 3%), abnormal dreams (1; 3%), dizziness (5; 16%), tinnitus (1; 3%)	Bentley & Head (1987)
< 1	General Surgery	10	Somnolence (7; 70%), nervousness (1; 10%), headache (1; 10%), depression (1; 10%)	Forbes et al (1984b)
< 1	Orthopaedic surgery	43	Headache (8; 19%), nausea (8; 19%), sweat (2; 5%), thirst (3; 7%), vomiting (4; 9%), amblyopia (1; 2%)	McQuay et al (1986)
< 1	Surgery	9	Headache (2; 22%), somnolence (7; 78%)	Jain et al (1986b)
< 1	Dental extractions	1	Headache (1; 100%)	Sunshine et al (1986)
< 1	Headache	226	Dizziness (33; 15%), dyspepsia (112; 50%), nervousness (23; 10%)	Migliardi et al (1994)
1	Dental extractions	16	Urination (1; 6%), chills (3; 19%), fever (1; 6%), headache (5; 31%), nausea (1; 6%); somnolence (3; 19%), vomiting (1; 6%), bleeding (1; 6%)	Nystrom et al (1988)
1	Dental extractions	7	Somnolence (1; 14%), abdominal pain (1; 14%), nausea (2; 29%), headache (1; 14%), agitation (1; 14%), dizziness (1; 14%)	Quiding et al (1982b)
1	Dental extractions	6	Somnolence (2; 33%), headache (1; 17%), abdominal pain (1; 17%), back pain (1; 17%), ear pain (2; 33%)	Quiding et al (1982a)
1	Migraine	3	Nausea (1; 33%), vomiting (1; 33%), dyspepsia (1; 33%)	Pearce et al (1983)
1	Febrile seizure	8	Hypothermia (1; 13%), rash (2; 25%), convulsions (3; 38%), gastrointestinal dis (2; 25%)	Van Esch et al (1995)
1	Dental extractions	3	Asthenia (1; 33%), headache (2; 67%)	Quiding et al (1981)
1	Oral surgery	5	Somnolence (2; 40%), nausea (1; 20%), dry mouth (1; 20%), headache (1; 20%)	Gallardo & Rossi (1990)
1	Migraine	1	Somnolence (1; 100%)	MacGregor et al (1993)
2	Tonsillitis, pharyngitis	3	Nausea (3; 100%)	Bertin et al (1991)
2	Fever	2	Vomiting (2; 100%)	Weippl et al (1985a)
3	Dental extractions	11	Headache (5; 45%), nausea (1; 9%), somnolence (4; 36%), vomiting (1; 9%)	Skoglund & Skjelbred (1984)

(continued)

Table 3. (continued)

Days dosed	Indication	Total adverse events	Costart term*	Reference
4	Rheumatoid arthritis	1	Site reaction (1; 100%)	Di Munno & Sarchi (1982)
5	Upper respiratory tract infection	14	Abdominal pain (1; 7%), somnolence (5; 36%), dry mouth (2; 14%), dizziness (1; 7%), gastrointestinal dis (5; 36%)	Middleton (1981)
5	Acute migraine	7	Somnolence (1; 14%), dizziness (1; 14%), constipation (1; 14%), diarrhoea (1; 14%), chest pain (1; 14%), sleep dis (1; 14%), asthenia (1; 14%)	Million et al (1984)
7	Lung disease	12	Somnolence (4; 33%), vomiting (1; 8%), pneumonia (1; 8%), pain (1; 8%), nausea (2; 17%), dyspnea (2; 17%), diarrhoea (1; 8%)	Munck et al (1990)
7	Cancer (Note: some adverse events might be related to disease state)	26	Dizziness (1; 4%), nausea (1; 4%), vertigo (2; 8%), tremor (2; 8%), sweating (3; 12%), somnolence (3; 12%), pruritus (2; 8%), gastrointestinal dis (1; 4%), agitation (2; 8%), dry mouth (3; 12%), constipation (1;4%), dyspepsia (3; 12%), headache (2; 8%)	Ventafridda et al (1990)
13	Stable chronic liver disease	1	Rash (1; 100%)	Benson et al (1983)
21	Hypertension	3	Headache (1; 33%), nervousness (1; 33%), Abnormal thoughts (1; 33%)	Radack et al (1987)
28	Osteoarthritis	19	Renal (1; 5%), rash (1; 5%), oedema general (1; 5%), nervous system (4; 21%), haematologic (1; 5%), genitourinary (1; 5%), gastrointestinal dis (10; 53%)	Bradley (1991)
30	Osteoarthritis	16	Diarrhoea (1; 6%), headache (1; 6%), nausea, vomiting (5; 31%), abdominal pain (6; 38%), pruritis (1; 6%), rash (1; 6%), anorexia (1; 6%)	Glorioso et al (1985)

*Values in brackets are number of adverse events and percentage of the total number of adverse events.

Table 4. Demographic distribution of adverse events for paracetamol and ibuprofen.

Days dosed	Drug	Percent with adverse events	Number with adverse events	Number of patients	Number of adverse events	Maximum age (years)	Reference
Children (<18 years)							
< 1	Ibuprofen	0	0	39	0	12	Schachtel & Thoden (1993)
< 1	Paracetamol	0	0	38	0	12	Schachtel & Thoden (1993)
< 1	Ibuprofen	0	0	20	0	12	Kauffman et al (1992)
< 1	Paracetamol	0	0	8	0	12	Kauffman et al (1992)
< 1	Ibuprofen	0	0	14	0	12	Moore et al (1985)
< 1	Paracetamol	0	0	11	0	12	Moore et al (1985)
1	Ibuprofen	1	1	93	1		Marriott et al (1991)
1	Ibuprofen	18	6	34	6	4	Van Esch et al (1995)
1	Paracetamol	22	8	36	8	4	Van Esch et al (1995)
2	Paracetamol	4	3	78	3	12	Bertin et al (1991)
2	Paracetamol	3	2	60	2	12	Weippl et al (1985a)
2	Paracetamol	0	0	56	0	12	Weippl et al (1985b)
5	Paracetamol	0	0	32	0	15	Breese Hall et al (1987)
5	Paracetamol	0	0	25	0	12	Thompson et al (1987)

Days dosed	Drug	Percent with adverse events	Number with adverse events	Number of patients	Number of adverse events	Minimum age (years)	Maximum age (years)	Reference
Aged (> 60 years)								
2	Paracetamol	0	0	39	0	–	–	Gross et al (1994)
7	Ibuprofen	0	0	8	0	60	–	Furey et al (1993)
7	Paracetamol	0	0	8	0	60	–	Furey et al (1993)
7	Ibuprofen	0	0	11	0	60	80	Malandrino et al (1987)
84	Ibuprofen	0	0	16	0	65	–	Ghosh & Rastogi (1982)
84	Ibuprofen	33	5	15	5	65	84	Admani & Verma (1983)

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Table 5. Comparison of adverse events, treatments and study type in studies where ibuprofen treatment was for ≤ 7 days.

Dose regimen for ibuprofen [study duration] study type	(Formulation) [Comparator (s)]*	Comments†	Total number of subjects
400 mg tid** [5 days]; gastrointestinal blood loss	[A; clonixinate lysine]	Gastrointestinal blood loss from ^{51}Cr-RBCs	6
200 mg [2 h]; sore throat‡‡	(Motrin); 2 doses	Ibuprofen effective; lower time for remedication	9
400 mg‡‡	(Motrin); 2 doses	(As above)	10
400 mg pressure headache at high altitude‡‡	–	1/12 Vomited with drug; 1/12 with placebo	20
25 mg tid [4 h]; antipyretic efficacy in uncomplicated falciparum malaria‡‡	[P 4 × 1000 mg day^{-1}]	Pre-treated with mefloquine (750, 500 mg); M	21
400 mg [1·5 h]; pain from CO_2 gas applied inside nostril‡‡	(Aktren)	–	18
800 mg‡‡ (as above)	(Aktren)	–	18
400 mg [3 h]; 3rd molar extraction‡‡	[D Na 50 mg]	5 ADR events observed; data insufficient; L (onset)	80§§
200 mg [8 h]; 3rd molar extraction‡‡	[M 50 & 100 mg]	–	51§§
400 mg (as above)	[M 50 & 100 mg]	–	49§§
5 × 200 mg day^{-1} 6 × 200 mg day^{-1} 6 days (as above)‡‡	[M 50 & 100 mg]	E (highest dose and high-dose meclofenamate)	59§§
5 × 400 mg day^{-1} 6 × 400 mg day^{-1} 6 days (as above)‡‡	[M 50 & 100 mg]	Bleeding at surgical site	57§§
3 × 200 mg [12 h]; dental surgery impaction‡‡	[C 30 mg]	M	45§§
600 mg (controlled release tablet)‡‡ (as above)	(I-controlled release) (as above)	Controlled-release superior analgesic	38
2 × 400 mg [10 h]; 3rd molar extraction‡‡	[I + C 60 mg]	L	69§§
≤4 × 400 mg day^{-1} [10 h], ≤6 days (as required); 3rd molar extraction‡‡	(Boots) [dihydro-C 30, 60 mg]	M	41§§
200 mg [4 h]; dental extraction‡‡	(Aluminium) [P 240 or 360 mg; P 240 mg + C 24 mg]	E	14
400 mg [6 h]; sore throat‡‡	[P 1000 mg]	M	39
1200 mg day^{-1} (400 mg tid × 4 days [4d]; joint sprains‡‡	(Brufen) [S 400 mg bd]	E	83§§
10 mg kg^{-1} tid × 2 days; tonsillitis/pharyngitis‡‡	(Microgranules or sparklets) [P 10 mg kg^{-1} tid × 2 days]	M	77§§
400 mg [8 h]; 3rd molar extraction‡‡	[A 650 mg, B 10–100 mg]	M (to all but higher doses of bromphenac)	45§§

Gastrointestinal adverse drug reactions			CNS Total (%)	Other Total (%)	Total (%)	Total adverse drug reaction events	Total adverse drug reaction subjects	Reference
Non nausea and vomiting‡	Nausea and vomiting§	Total (%)						
Observed DC; SD; H	0·00	0·00	0·00	0·00	††	7	6	Bidlingmaier et al (1995)
0·00	0·00	0·00	0·00	0·00	0·00	0	0	Schachtel et al (1994)
0·00	0·00	0·00	0·00	0·00	0·00	0	0	Schachtel et al (1994)
0·00	5·00 V	5·00	10·00	0·00	15·00	3	2	Broome et al (1994)
0·00	0·00	0·00	0·00	0·00	0·00	0	0	Wilairatana & Looaresuwan (1994)
0·00	0·00	0·00	0·00	0·00	0·00	0	0	Kobal et al (1994)
0·00	0·00	0·00	0·00	0·00	0·00	0	0	Kobal et al (1994)
††	††	††	††	††	††	††	6	Bakshi et al (1994)
0·00	0·00	0·00	7·84	0·00	7·84	4	4	Hersh et al (1993)
0·00	2·04 V; 2·04 N	4·08	8·16	2·04	14·28	7	6	Hersh et al (1993)
0·00	1·69 V; 10·17 N	11·86	30·50	3·38	45·74	27	19	Hersh et al (1993)
1·75 DC; 1·75 SD	1·75 V; 14·04 N	19·29	28·06	10·51	57·86	33	18	Hersh et al (1993)
††	11·11 N	11·11	††	††	††	30	††	Cooper et al (1993)
††	2·22 N	2·22	††	††	††	16	††	Cooper et al (1993)
0·00	4·35 N	4·35	4·35	0·00	8·70	7	6	Petersen et al (1993)
0·00	2·44 V; 7·32 N	9·76	14·64	7·32	31·72	13	8	McQuay et al (1993)
0·00	0·00	0·00	0·00	0·00	0·00	0	0	Moore et al (1985)
0·00	0·00	0·00	0·00	0·00	0·00	0	0	Schachtel et al (1988)
0·00	0·00	0·00	0·00	0·00	0·00	0	0	Bouchier-Hayes et al (1984)
Observed SD	Observed	0·00	0·00	0·00	††	††	5	Bertin et al (1991)
2·22 SD	0·00	2·22	13·32	2·22	17·76	8	4	Forbes et al (1992)

(continued)

Table 5. *(continued)*.

Dose regimen for ibuprofem [study duration] study type	(Formulation) [Comparator (s)]*	Comments†	Total number of subjects
2·5/5/10 mg kg^{-1} qid × 1–2 days; antipyretic in febrile children‡‡	[P 4 × 15 mg kg day^{-1} × 1–2 d]	E	48§§
7·5/10 mg kg^{-1} [8 h]; fever reduction in febrile children‡‡	[P 10 mg kg^{-1}]	M	20
400 mg [6 h]; post-orthopaedic surgery‡‡	[P 300 mg + C 30 mg]	M; overall occurrence of ADRs = 15%	40§§
50 mg [8 h]; 3rd molar extraction‡‡	[I 100 mg + caffeine 100 mg; I 200 mg + caffeine 100 mg	L	63§§
100 mg‡‡; (as above)	(As above)	L	62§§
200 mg‡‡; (as above)	(As above)	L	60§§
400 mg [2 h]; 3rd molar extraction‡‡	[2 × P 500 mg + C 8 mg + caffeine 30 mg (Solpadeine); 2 × A 300 mg + 30 mg caffeine (Anadin); dihydro-C tartrate 30 mg]	E (combinations) M (dihydro-C)	26
400 mg [6 h]; dental impaction surgery‡‡	[P 1000 mg]	M	63§§
400 mg [6 h]; 3rd molar extraction‡‡	[D dispersible 50 mg]	E	32
400 mg [2 h]; muscle-contraction headaches‡‡		Early onset of action	35
400 mg [4 h]; pain after episiostomy ‡‡	[P 1000 mg]	M	36
400 mg day^{-1} tid × 6 days, as required; 3rd molar extraction‡‡	[C base 20 mg + I 400 mg]	L	23
400 mg [6 h]; 3rd molar extraction*	(Soft gelatine/ tablets (Nurofen)/ soluble]	–	93§§
400 mg [1 day]; pharmacokinetic study	(Iburo/Burana)	L (Iburo absorption)	10
400 mg [6 h]; oral surgery‡‡	[P 1000 mg]	M	310§§
600 mg tid ×7 days [7d]; cancer‡‡	[A 600 mg tid; P 500 mg tid; D slow release bd + placebo; indomethacin 50 mg tid; pirprofen 400 mg tid; S 300 mg bd + placebo; N 250 mg tid; suprofen 200 mg tid]	M (paracetamol); Naproxen, diclofenac, indomethacin; highly effective & well tolerated	13
6 × 200 mg day^{-1} [24 h]; coxarthrosis‡‡	[I 200 mg + C 30 mg]	L	26
200 mg [2 h]; endoscopic evaluation of gastroduodenal mucosa	[K 25 mg; A 500 mg]	Mucosal lesions lower with I and K than with A	12
400 mg [4 h]; episiotomy, caesarean section, or gynaecological surgery‡‡	[I 400 mg + C 60 mg; I 200 mg + C 30 mg; C-sulphate]	L (high-dose combination), E (low); M (C-sulphate)	38

Gastrointestinal adverse drug reactions			CNS Total (%)	Other Total (%)	Total (%)	Total adverse drug reaction events	Total adverse drug reaction subjects	Reference
Non nausea and vomiting‡	Nausea and vomiting§	Total (%)						
6·25 SD; 14·58 G	6·25V; 6·25 N	33·33	0·00	16·67	50·00	16	††	Walson et al (1992)
0·00	0·00	0·00	0·00	0·00	0·00	0	0	Kauffman et al (1992)
††	††	††	††	††	††	††	††	Heidrich et al (1985)
††	1·59 V; 1·59 N	3·18	17·46	3·18	23·82	15	10	Forbes et al (1991a)
0·00	0·00	0·00	9·68	0·00	9·68	6	5	Forbes et al (1991a)
0·00	3·33 V	3·33	6·67	0·00	10·00	6	6	Forbes et al (1991a)
0·00	0·00	0·00	0·00	0·00	0·00	0	0	Habib et al (1990)
0·00	0·00	0·00	11·11	0·00	11·11	6	5	Cooper et al (1989)
††	††	††	3·13	0·00	††	††	3	Ahlstrom et al (1993)
0·00	0·00	0·00	0·00	0·00	0·00	0	0	Schachtel & Thoden (1988)
0·00	0·00	0·00	0·00	0·00	0·00	0	0	Schachtel et al (1989)
0·00	4·35 N	4·35	13·05	0·00	17·40	4	3	McQuay et al (1989)
0·00	0·00	0·00	0·00	0·00	0·00	0	0	Seymour et al (1991)
0·00	0·00	0·00	20·00	0·00	20·00	2	2	Karttunen et al (1990)
5·16 G	0·00	5·16	3·56	0·00	8·72	27	31	Mehlisch et al (1990)
7·69 BL; 7·69 N 23·08 H	7·69 N	38·46	53·83	69·23	161·52	21	††	Ventafridda et al (1990)
Observed SD	11·54 N	11·54	0·00	0·00	††	5	††	Quiding et al (1992)
††	††	††	††	††	††	††	††	Bergmann et al (1992)
0·00	0·00	0·00	0·00	0·00	0·00	0	0	Sunshine et al (1987)

(continued)

Table 5. *(continued)*.

Dose regimen for ibuprofem [study duration] study type	(Formulation) [Comparator (s)]*	Comments†	Total number of subjects
5 mg kg^{-1} qid × 1–3 day; antipyretic in febrile children‡‡	(Syrup) [P (syrup) 10 mg kg^{-1} day^{-1}]	M	34
0·625 mg kg^{-1} [3 h]; antipyretic‡‡	(Suspension)	Dose-related antipyretic effect	26
1·25 mg kg^{-1}; (as above)	(Suspension)	Dose-related antipyretic effect	24
2·5 mg kg^{-1}; (as above)	(Suspension)	Dose-related antipyretic effect	26
5·0 mg kg^{-1}; (as above)	(Suspension)	Dose-related antipyretic effect	24
10 mg kg^{-1} [6 h]; sore throat‡‡	[P 15 mg kg^{-1}]	E	39
400 mg day^{-1} tid [48 h]; sleep patterns	[A 650 mg tid; P 650 mg tid]	Disrupted sleep patterns	9
400 mg tid [7 days]; primary dysmenorrhea‡‡	(Motrin) [Indomethacin (Indocin) 25 mg]	M	31
100 mg [6 h]; impacted tooth extraction‡‡	[A 650 mg]	E	39
200 mg; (as above)	[A 650 mg]	E	47§§
400 mg; (as above)	[A 650 mg]	E	49§§
400 mg [8 h]; 3rd molar extraction‡‡	[B 5/10/25 mg; A 650 mg]	M (all but bromfenac 25 mg)	43§§
600 mg day^{-1} tid × 7 days [7d]; endoscopic study	[A 500 mg; indomethacin 25 mg; phenylbutazone 200 mg]	All produced dyspeptic symptoms	5
400 mg day^{-1} tid × 7 days [7d]; renal function in rheumatoid arthritis	[Suprofen 200 mg tid × 7 days]	Renal function unimpaired; decreases in prostaglandin levels	11
400 mg day^{-1} tid × 7 days; renovascular effects	[A 650 mg tid × 7 days; P 650 mg tid × 7 days]	N	8
400 mg [4 h]; dental impaction surgery‡‡	[C 60 mg; A 650 mg; I 400 mg; A 650 mg + C 60 mg, I 400 mg + C 60 mg]	M (aspirin)	38
400 mg tid × 7 days [7d]; sports injury‡‡	[S 200 mg bd × 7 days]	L	14
1–12 × 400 mg within 4 days, as required [4d]; post-operative foot pain‡‡	[1–12 × P 300 mg + C 30 mg within 4 days, as required]	E	36
200 mg [6 h] ADRs profile	[P 650/1000 mg]	–	171§§
400 mg (as above)	[P 650/1000 mg]		707§§
600 mg [5 h]; strabismus surgery‡‡	[P 650 mg; ketorolac 60 mg i.v.]	L	20
400 mg every 6 h [72 h]; postinstrumentation of root canals‡‡	(Motrin) [A 650 mg; P (Tylenol) 650 mg; K (Orudis) 50 mg; P 325 mg + C 60 mg (Phenaphen #4); penicillin (Veetids) 500 mg; erythromycin base 500 mg; penicillin 500 mg + I 400 mg; methylprednisolone (MedRol) 2 mg + penicillin 500 mg]	1·8% Of subjects had ADRs though data insufficient to catagorize; N (with mild pain)	57

Gastrointestinal adverse drug reactions			CNS Total (%)	Other Total (%)	Total (%)	Total adverse drug reaction events	Total adverse drug reaction subjects	Reference
Non nausea and vomiting‡	Nausea and vomiting§	Total (%)						
0·00	0·00	0·00	2·94	5·88	8·82	6	0	Van Esch et al (1995)
0·00	3·85 N	3·85	0·00	0·00	3·85	2	2	Marriott et al (1991)
0·00	0·00	0·00	8·34	0·00	8·34	3	3	Marriott et al (1991)
0·00	3·85 N	3·85	15·39	3·85	23·09	7	6	Marriott et al (1991)
4·17 DC	12·50 N	16·67	4·17	0·00	20·84	7	6	Marriott et al (1991)
0	2·56 V	2·56	0	0	2·56	1	1	Schachtel & Thoden (1993)
††	††	††	††	††	††	††	††	Murphy et al (1994)
0·00	0·00	0·00	0·00	0·00	0·00	0	0	Gookin et al (1983)
2·56 H	5·13 V; 7·69 N	15·38	17·96	5·12	38·46	15	13	Jain et al (1986a)
0·00	6·38 N	6·38	4·26	6·39	17·03	8	6	Jain et al (1986a)
0·00	2·04 V	2·04	18·36	4·08	24·48	12	10	Jain et al (1986a)
0·00	2·33 N	2·33	16·30	0·00	18·63	8	7	Forbes et al (1991a)
††	††	††	††	††	††	††	††	Puscus et al (1989)
††	††	††	††	††	††	††		Malandrino et al (1987)
0·00	0·00	0·00	0·00	0·00	0·00	0	0	Furey et al (1993)
0·00	0·00	0·00	26·31	5·26	31·57	12	11	Cooper et al (1982)
7·14 G	0·00	0·00	0·00	7·14		1	1	Walker et al (1984)
2·78 DC	2·78 N	5·56	2·78	11·12	19·46	7	4	Wittenberg et al (1984)
2·34 SD; 2·34 H§§	2·34 N	7·02	2·33	1·16	10·51	9	8	Furey et al (1992)
0·57 SD; 0·57 H	0·57 N	1·70	1·98	0·14	3·82	17	13	Furey et al (1992)
0·00	10·00 N	10·00	0·00	0·00	10·00	1	1	Morrison & Repka (1994)
††	††	††	††	††	††	††	††	Torabinejad et al (1994)

Table 5. *(continued)*.

Dose regimen for ibuprofem [study duration] study type	(Formulation) [Comparator (s)]*	Comments†	Total number of subjects
400 mg [4 h]; suction termination of pregnancy‡‡	(L-arginine)		38
Dose? [4 h] tension-type headache‡‡	(L-arginine, sachet) [β-cyclodextrin piroxicam; dose?]	E; those with nausea usually suffered it with headache anyway	26
400 mg [6 h]; caesarean section‡‡†	(L-arginine) [ketorolac 30 mg orally]		30
400 mg [6 h]; post-operative pain‡‡	(L-arginine) [ketorolac 30 mg orally]		42§§
400 mg qid × 7 days [7d]; rheumatism‡‡	[F-calcium 4 × 600 mg day^{-1} × 7 days]	N (except where limitation of movement concerned)	50§§
400 mg [5 h]; dental surgery‡‡	(L-arginine, sachet) [N-sodium 550 mg]	E; involved some bone surgery	46§§
400 mg tid [7 d]; rheumatoid arthritis‡‡	[Indomethacin slow release 50 mg bd]	Reduction in duration of morning stiffness; aspirin used as rescue analgesic	22
		Totals:	3571
			Mean%:
			± s.d.:
			Median:
			Maximum:
			Minimum:

Adverse drug reactions are expressed as a percentage of the total number of subjects. *(A) aspirin, (B) bromfenac, (C) codeine, (D) diclofenac, (F) fenoprofen, (I) ibuprofen, (K) ketoprofen, (M) meclofenamate, (N) naproxen, (P) paracetamol, (S) sulindac. †(M) more, (L) less effective than comparator; (E) equiactive, (N) No effect, (ADR) adverse drug reaction· ‡(BL) blood loss, (H) heartburn, (DC) diarrhoea/constipation, (SD) discomfort, (G) general. §(N) nausea, (V) vomiting· **'tid' — three times daily; 'qid' — four times daily· ††indicates that no adverse drug reactions were mentioned. ‡‡ Clinical trials. §§n ≥ 40.

Gastrointestinal adverse drug reactions			CNS Total (%)	Other Total (%)	Total (%)	Total adverse drug reaction events	Total adverse drug reaction subjects	Reference
Non nausea and vomiting‡	Nausea and vomiting§	Total (%)						
0·00	2·632 V	2·63	0·00	0·00	2·63	1	1	Pagnoni et al (1996a)
0·00	3·85 N	3·85	0·00	0·00	3·85	1	1	Laveneziana et al (1996a)
0·00	0·00	0·00	0·00	0·00	0·00	0	0	Pagnoni et al (1996b)
0·00	0·00	0·00	0·00	0·00	0·00	0	0	Laveneziana et al (1996a)
2·00 SD; 6·00H	1·00 V; 4·00 N	13·00	0·00	0·00	13·00	7	4	Williams (1983)
0·00	0·00	0·00	2·17	0·00	2·17	1	1	Borea et al (1996)
4·55 SD	4·55 V; 4·55N	13·64	13·64	0·00	27·28	6	5	Gordin et al (1985)
						395	253	
0·14 BL; 0·15 DC; 0·34 SD; 0·47 G; 0·60 H	1·60 (0·72V; 2·46 N)	4·66	6·54	2·63	13·95			
1·03 BL; 0·69 DC; 1·12 SD; 2·23 G; 3·14 H	3·02 (1·50 V; 3·80 N)	7·61	10·10	9·33	23·96			
0·00 BL, DC, SD, G, H	0·00 V, N	2·04	2·08	0·00	8·52			
7·69 BL; 4·17 DC; 6·25 SD; 14·58 G; 23·08 H	14·04 (6·25 V; 14·04 N)	38·46	53·83	69·23	161·52			
0·00 BL, DC, SD, G, H	0·00 V, N	0·00	0·00	0·00	0·00			

Table 6.   Comparison of adverse events, treatments and study type in studies where paracetamol treatments were for ≤ 7 days.

Dose regimen for ibuprofen [study duration] study type	(Formulation) [Comparator(s)]*	Comments†	Total number of subjects
1000 mg [4 h]; tension headache‡‡	[P 500 mg + A 500 mg + caffeine 130 mg; P 1000 mg + caffeine 130 mg]	L	2091§§
650 mg [8 h]; antipyretic in endotoxin-induced fever‡‡	[ketorolac 15/30/60 mg orally]	E; 378 ADR events observed but unable to relate cause with type	30
100 mg qid** [4 h]; antipyretic in uncomplicated falciparum malaria‡‡	[I 25 mg tid**]	L; pre-treated with mefloquine (750 & 500 mg)	21
1000 mg (4 h)$^{-1}$ or (attack)$^{-1}$ ($\leq 4 \times$) as required [24 h]; migraine‡‡	[Domperidone 30 mg + P 1000 mg (4 h)$^{-1}$ (attack)$^{-1}$ (max 4×) as required; domperidone 20 mg + P 1000 mg (4 h)$^{-1}$(attack)$^{-1}$ (max 4×) as required]	L	46§§
10 mg kg^{-1} day^{-1} or (6 h)$^{-1}$ ≤ 360 mg day^{-1} maximum [5 days]; influenza A infection‡‡	[Rimantadine 6·6 mg kg^{-1} day^{-1} or (12 h)$^{-1}$ up to 200 mg day^{-1} max]	E	34
500 mg [4 days]; wisdom tooth extraction‡‡	[Suprofen 200 mg (Suprocil)]	E	29
1000 mg tid followed by 4 × 500 mg day^{-1} × 2 days [7 days]; oral surgery‡‡	[Methylprednisolone (Medrol) 24/20/16/12/8/4 mg in decreasing doses up to 1 day post-surgery]	> 3 ADR events observed, but data insufficient to relate drug with event.); M	24
650 mg [6 h]; 3rd molar extraction‡‡	[Flurbiprofen (Ansaid) 50/100 mg; zomepirac sodium 100 mg; P 650 mg + C-phosphate 60 mg]	E (combination); L (others)	30
650 mg [6 h]; post-operative pain‡‡	[Nalbuphine 30 mg; P 650 mg + nalbuphine 30 mg]	L	30
50/200/400 mg (tid max) depending on age & weight [6 h]; antipyretic activity‡‡	[Suprofen (Suprol) syrup 50/100/200 mg (tid max) depending on age and weight	L	59§§
125/250/250 + 125/ 500/500 + 125/500 + 250 mg (tid max) depending on weight [6 h]; antipyretic activity‡‡	[Suprofen (Suprol) suppository 50/100/100 + 50/200/200 + 50 mg (tid max) depending on weight]	2 ADR events observed, but data insufficient; L	60§§
500 mg [6 h]; pain from orthopaedic operation‡‡	[Ketorolac 5/10/20 mg]		30
1000 mg; (as above)	[Ketorolac 5/10/20 mg]	L (high doses of ketoprofen)	30
240/360 mg [4 h]; dental extraction in children‡‡	[I (Aluminium); P 240 mg + C 24 mg]	E	11
Up to 1000 mg qid ×5 days [5 days]; migraine‡‡	[Flupirtine maleate up to 100 mg day^{-1} × 5 days as required]	L	20
1000 mg [6 h]; sore throat‡‡	[I 400 mg]	L	40§§
1000 mg qid, then 500 mg qid × 2 days [4 days]; oral surgery‡‡	(Panadol) [2 × P 1000 mg + P-N-acetyl-DL-methionate (SUR2647) 2146 mg day^{-1} followed by 2 × P 500 mg + SUR2647 1073 mg day^{-1} × 2 days]	L	26
650 mg [4 h]; post-operative pain‡‡	[Nalbuphine hydrochloride 30 mg; nalbuphine HCl 30 mg + P 650 mg]	Analgesic efficacy of combination additive	33

Gastrointestinal adverse drug reactions			CNS Total (%)	Other Total (%)	Total (%)	Total adverse drug reaction events	Total adverse drug reaction subjects	Reference
Non nausea and vomiting‡	Nausea and vomiting§	Total (%)						
5·36 SD	0·00	5·36	2·68	10·81	18·85	3	226	Migliardi et al (1994)
††	††	††	††	††	††	††	††	Vargas et al (1994)
0·00	0·00	0·00	0·00	0·00	0·00	0	0	Wilairatana & Looaresuwan (1994)
0·00	0·00	0·00	2·17	0·00	2·17	1	1	MacGregor et al (1993)
0·00	2·94 N	2·94	0·00	2·94	5·88	2	2	Thompson et al (1987)
0·00	0·00	0·00	3·45	3·45	6·90	2	2	Reijntjes et al (1987)
††	††	††	††	††	††	††	3	Olstad & Skjelbred (1986)
0·00	0·00	0·00	3·33	0·00	3·33	1	1	Sunshine et al (1986)
0·00	0·00	3·33	26·66	3·33	33·32	9	9	Jain et al (1986b)
0·00	5·08 V	5·08	0·00	0·00	5·08	3	3	Weippl et al (1985b)
††	††	††	††	††	††	††	††	Weippl et al (1985a)
0·00	3·33 V; 6·67 N	10·00	10·00	40·00	60·00	18	15	McQuay et al (1986)
0·00	10·00 V; 20·00 N	30·00	16·67	36·66	83·33	25	17	McQuay et al (1986)
0·00	0·00	0·00	0·00	0·00	0·00	0	0	Moore et al (1985)
10·00 DC	0·00	10·00	20·00	5·00	35·00	7	5	Million et al (1984)
0·00	0·00	0·00	0·00	0·00	0·00	0	0	Schachtel et al (1988)
0·00	3·85 V; 3·85 N	7·70	34·61	0·00	42·31	11	8	Skoglund & Skjelbred (1984)
0·00	0·00	0·00	30·30	0·00	30·30	10	9	Forbes et al (1984b)

(continued)

Table 6   (continued)

Dose regimen for ibuprofen [Study duration] Study type	(Formulation) [Comparator(s)]*	Comments†	Total number of subjects
1000 mg [5 h]; oral surgery‡‡	[C 60 mg; P 1000 mg + C 60 mg]	L	42§§
650 mg [6 h]; episiotomy, surgical or dental procedures‡‡	[Flupirtine 100/200/ 300 mg; C 60 mg; pentazocine 50 mg/ oxycodone 10 mg + P 650 mg]		††
10 mg kg^{-1} tid × 2 days [2 days]; tonsil-itis/pharyngitis‡‡	[I 10 mg kg^{-1} tid × 2 days (microgranules or sparklets)]	L	78§§
1000 mg [4 h]; muscle contraction headache‡‡	[A 1000 mg + caffeine 64 mg]	L	100§§
15 mg kg^{-1} qid × 1–2 days; antipyretic‡‡	[I 4 × 2·5/5/10 mg kg^{-1} day^{-1} × 1–2 days]	E	16
10 mg kg^{-1} [8 h]; antipyretic‡‡	[I 7·5/10 mg kg^{-1}]	L	8
2× 1000 mg [10 h]; 3rd molar extraction	[Diflunisal 500 mg]	One dose paracet-amol pre- & one 4 h post-operative diflusinal pre-operative; N	35
1000 mg [6 h]; dental impaction surgery‡‡	[I 400 mg]	L	63§§
650 mg [6 h]; episiotomy	[P 650 mg + phenyltoloxamine citrate 60 mg]	L	75§§
1000 mg [4 h]; episiotomy‡‡	[I 400 mg]	L	37
1000 mg [6 h]; oral surgery‡‡	[I 400 mg]	L	307§§
500 mg tid ×7 days; cancer‡‡	[I 600 mg tid; A 600 mg tid; D slow release bd + placebo; indomethacin 50 mg tid; pirprofen 400 mg tid; sulindac 300 mg bd + placebo; N 250 mg tid; suprofen 200 mg tid, all × 7 days]	L	13
1000 mg [7 days]; chronic obstructive lung disease‡‡	[C 60 mg + P 1000 mg]	More gastrointestinal ADRs in combination	18
500 mg qid × 1 day [24 h]; periodontal surgery‡‡	[4 × 100 mg day^{-1} flurbiprofen]	L	15
10 mg kg × 5 days [5 days]; infection by influenza A‡‡	[6·6 mg kg^{-1} × 5 days rimantadine]	L	32
650 mg [12 h]; muscle contraction headache‡‡	(Tylenol) [N-sodium (Anaprox) 550 mg]	L	50§§
250 mg qid × 5 days [5 days]; common cold/upper respiratory tract infection‡‡	[3 × P 500 mg + phenylpropanolamine 25 mg & 1 × P 500 mg + diphenhydramine hydrochloride 25 mg ('Benylin Day & Night') day^{-1} × 5 days]	L	90§§
1000 mg [6 h]; orthopaedic operations‡‡	[Tiaramide hydrochloride 100/200 mg]	M	21
500 mg (2 h)$^{-1}$ × 10 h as required; lower wisdom tooth removal‡‡	[5 × C-phosphate 30 mg + A 300 mg + P 200 mg + caffeine 50 mg + magnesium oxide 25 mg (Staralgin) (2 h)$^{-1}$ × 10 h as required; 5 × dextropro-poxyphene napsylate 100 mg + A350 mg + phenazone 150 mg (Doleron novum) (2 h)$^{-1}$ × 10 h as required]	L (Doleron novum); E E (codeine)	27

Gastrointestinal adverse drug reactions			CNS Total (%)	Other Total (%)	Total (%)	Total adverse drug reaction events	Total adverse drug reaction subjects	Reference
Non nausea and vomiting‡	Nausea and vomiting§	Total (%)						
2·38 SD	14·29 V; 16·67 N	33·34	38·08	2·38	73·80	31	21	Bentley & Head (1987)
Observed	††	††	††	††	††	††	18	McMahon et al (1987)
0·00	3·85 N	3·85	0·00	0·00	3·85	3	3	Bertin et al (1991)
0·00	0·00	0·00	0·00	0·00	0·00	0	0	Schachtel et al (1991)
18·75 SD	0·00	18·75	18·75	18·75	56·25	9	††	Walson et al (1992)
0·00	0·00	0·00	0·00	0·00	0·00	0	0	Kauffman et al (1992)
0·00	0·00	0·00	0·00	0·00	0·00	0	0	Rodrigo et al (1989)
0·00	3·17 N	3·17	15·87	0·00	19·04	13	11	Cooper et al (1989)
0·00	0·00	0·00	0·00	0·00	0·00	0	0	Sunshine et al (1989)
0·00	0·00	0·00	0·00	0·00	0·00	0	0	Schachtel et al (1989)
4·23 G	0·00	4·23	6·51	0·00	10·74	33	32	Mehlisch et al (1990)
7·69 DC; 30·77 H	7·69 N	46·15	69·22	76·91	192·30	26	††	Ventafridda et al (1990)
5·56 DC	5·56V; 11·11 N	22·23	22·22	22·23	66·68	12	10	Munck et al (1990)
0·00	6·67 N	6·67	20·00	6·67	33·34	5	††	Gallardo & Rossi (1990)
0·00	0·00	0·00	0·00	0·00	0·00	0	0	Breese Hall et al (1987)
2·00 DC	2·00 N	4·00	4·00	2·00	10·00	5	4	Miller et al (1987)
1·11 DC; 6·67 SD; 5·56 H	5·56N	18.90	6·67	2·22	27·79	14	11	Middleton (1981)
0·00	4·76 N	4·76	0·00	0·00	4·76	1	1	Winnem et al (1981)
0·00	3·70 N	3·70	11·11	0·00	14·81	4	3	Quiding et al (1981)

Table 6 (continued)

Dose regimen for ibuprofen [Study duration] Study type	(Formulation) [Comparator(s)]*	Comments†	Total number of subjects
650 mg [6 h]; 3rd molar extraction‡‡	[Flurbiprofen 50/100 mg; P 650 mg + C 60 mg]	L (Flurbiprofen); E (combination)	27
10 mg kg⁻¹ qid × 1–3 days; antipyretic‡‡	[I 4 × 5 mg kg⁻¹ day⁻¹ × 1–3 days]	L	36
15 mg kg⁻¹ [6 h]; sore throat‡‡	[I 10 mg kg⁻¹]	E	38
650 mg day⁻¹ tid [48 h]; effect on sleep patterns	[I 400 mg day⁻¹ tid]	Effect on sleep patterns	9
1000 mg [6 h]; headache‡‡	[A 650 mg]		87§§
500 mg (2 h)⁻¹ × 10 h as required; lower wisdom tooth extraction‡‡	[500 mg Phenazone (2 h)⁻¹ × 10 h; 500 mg phenazone + 100 mg dextropropoxyphene napsylate (2 h)⁻¹ × 10 h]	E	33
500 mg (2 h)⁻¹ × 10 h as required; lower wisdom tooth extraction‡‡	[P 500 mg + C 20 mg (2 h)⁻¹ × 10 h; P 500 mg + C 30 mg (2 h)⁻¹ × 10 h; P 500 mg + C 40 mg (2 h)⁻¹ × 10 h]		66§§
1000 mg [5 h]; postoperative pain‡‡	[C phosphate 60 mg; P 1000 mg + C phosphate 60 mg]		46§§
500 mg qid × 4 days [4 days]; post-endodontic periodontitis secondary to infiltrative/abscessed pulpitis‡‡	[100 mg Fentiazac qid × 4 days]	L (in patient, though not in investigator's assessment of induced pain)	14
1000 mg qid × 2 days; immune response to influenza vaccine‡‡	None	N	39
650 mg [6 h]; post-episiotomal pain‡‡	[Aceclofenac 100 mg]	L	30
650 mg day⁻¹ tid × 7 days; renovascular effects	[I 400 mg day⁻¹ tid × 7 days]	N	8
650 mg [6 h]; oral surgery‡‡	[Phenyltoloxamine 60 mg; P 650 mg + phenyltoloxamine 60 mg	M	43§§
1000 mg [4 h]; post-partum pain‡‡	[A 800 mg + caffeine 65 mg; P 648 mg + A648 mg]	M	123§§
650 mg [6 h] ADRs profile	[I 200/400 mg]		237§§
1000 mg; [6h] ADRs profile	[I 200/400 mg]		612§§
2000 mg day⁻¹ × 4 days; grip in rheumatoid arthritis	[Tolmetin 1200 mg day⁻¹ × 4 days]	L	12
600 mg [12 h]; 3rd molar extraction‡‡	[Flurbiprofen 100 mg; P 600 mg + C 60 mg]	L	26
650 mg [5 h]; post-strabismus surgery‡‡	[I 600 mg; Ketorolac 60 mg i.v.]	L (Ketorolac)	20
2 × 500 mg (10 h)⁻¹ as required; lower wisdom tooth extraction‡‡	[500 mg Diflunisal]	L	45§§
2 × 1000 mg (10 h)⁻¹ as required; lower wisdom tooth extraction‡‡	[500 mg Diflunisal]	L	46§§

Gastrointestinal adverse drug reactions			CNS Total (%)	Other Total (%)	Total (%)	Total adverse drug reaction events	Total adverse drug reaction subjects	Reference
Non nausea and vomiting‡	Nausea and vomiting§	Total (%)						
0·00	7·41 N	7·41	18·51	7·41	33·33	9	7	Dionne et al (1994)
5·56 G	0·00	5·56	0·00	2·78	8·34	8	0	Van Esch et al (1995)
0·00	0·00	0·00	0·00	0·00	0·00	0	0	Schachtel & Thoden (1993)
††	††	††	††	††	††	††	††	Murphy et al (1994)
8·05 G	0·00	8·05	0·00	6·90	14·95	13	††	Peters et al (1983)
3·03SD	0·00	3·03	15·15	9·09	27·27	9	5	Quiding et al (1982a)
1·52 G	3·03 N	4·55	6·08	0·00	10·63	7	6	Quiding et al (1982b)
2·17 SD; 2·17 H	2·17 V; 6·52 N	13·03	10·87	6·52	30·42	0	0	Gertzbein et al (1986)
0·00	0·00	0·00	0·00	0·00	0·00	0	0	Leguen (1985)
0·00	0·00	0·00	0·00	10·25	10·25	4	4	Gross et al (1994)
0·00	0·00	0·00	0·00	0·00	0·00	0	0	Movilia (1989)
0·00	0·00	0·00	0.00	0.00	0.00	0	0	Furey et al (1993)
0.00	0.00	0.00	2.33	0.00	2.33	2	1	Forbes et al (1984a)
0·00	0·00	0·00	4·88	0·00	4·88	6	6	Rubin & Winter (1984)
0·42 DC; 2·11 SD; 2·11 H	2·11 N	6·75	6·33	0·42	13·50	20	15	Furey et al (1992)
1·27 SD; 1·27 H	1·27 N	3·81	8·02	0·00	11·83	17	12	Furey et al (1992)
0.00	0.00	0·00	0·00	0·00	0.00	0	0	Di Munno & Sarchi (1982)
0·00	3·85 N	3·85	7·70	0·00	11·55	3	3	Forbes et al (1989)
0·00	10·00 N	10·00	0·00	0·00	10·00	1	1	Morrison & Repka (1994)
0·00	2·22 N	2·22	2·22	6·66	11·10	6	5	Nystrom et al (1988)
0·00	2.17 V	2·17	13·04	6·52	21·73	10	7	Nystrom et al (1988)

Table 6 (continued)

Dose regimen for ibuprofen [study duration] study type	(Formulation) [Comparator(s)]*	Comments†	Total number of subjects
650 mg per 6 h [72 h]; postinstrumentation of root canals‡‡	(Tylenol) [A 650 mg; I (Motrin) 400 mg; K (Orudis) 50 mg; P 325 mg + C 60 mg (Phenaphen #4); penicillin (Veetids) 500 mg; [erythromycin base 500 mg; penicillin 500 mg + I 400 mg; methylprednisolone (MedRol) 2 mg + penicillin 500 mg]	1·8% of subjects had ADRs though data insufficient to catagorize; E (with mild pain)	50§§
1000 mg qid × 5 days; laser-induced pain‡‡	(Plain)	Effective analgesic	15
2000 mg bd × 5 days; laser-induced pain‡‡	(slow release)	Effective analgesic	15
		Totals:	5348
		Mean%:	
		± s.d.:	
		Median:	
		Maximum:	
		Minimum:	

Table 7. Statistical analysis of selected data from Tables 5 and 6 (n ≥ 40, treatment ≤ 7 days) comparing adverse events of ibuprofen with those of paracetamol.

Adverse event	F	P	
Gastrointestinal			
Constipation	0·563	0·457	N/S
Vomiting	0·048	0·827	N/S
Discomfort	0·336	0·565	N/S
Nausea	0·460	0·501	N/S
Heartburn	0·161	0·690	N/S
General	0·044	0·835	N/S
Gastrointestinal total	0·0003	0·987	N/S
CNS total	0·704	0·406	N/S
Other total	0·055	0·816	N/S
Total	0·351	0·557	N/S

N/S, Not significant; analysis of variance single factor, level of significance set at 0·05.

Table 8. Comparison of adverse events from data denoted '§§' in Tables 5 and 6 in studies where ibuprofen and paracetamol were compared directly (n ≥ 40, treatment ≤ 7 days).

Adverse events	F	P	
Gastrointestinal			
Constipation	1·000	0·341	N/S
Discomfort	1·225	0·297	N/S
Vomiting	1·227	0·297	N/S
Nausea	0·006	0·941	N/S
Heartburn	0·001	0·975	N/S
General	1·060	0·328	N/S
Gastrointestinal total	0·639	0·443	N/S
CNS total	1·013	0·338	N/S
Other total	1·138	0·311	N/S
Total	0·733	0·414	N/S

N/S, Not significant; analysis of variance single factor, level of significance set at 0·05·

Gastrointestinal adverse drug reactions			CNS Total (%)	Other Total (%)	Total (%)	Total adverse drug reaction events	Total adverse drug reaction subjects	Reference
Non nausea and vomiting‡	Nausea and vomiting§	Total (%)						
††	††	††	††	††	††	††	††	Torabinejad et al (1994)
0·00	0·00	0·00	0·00	0·00	0·00	0	0	Nielsen et al (1991)
0·00	6·67 N	6·67	6·67	0·00	13·34	2	1	Nielsen et al (1991)
						365	488	
0·00 BL; 0·49 DC; 0·76 SD; 0·35 G; 0·76 H	1·71 (0·84 V; 2·58 N)	5·84	8·44	5·27	19·55			
0·00 BL; 1·84 DC; 2·78 SD; 4·21 H; 1·42 G;	3·61 (2·57 V; 4·26 N)	9.15	12.79	12.79	31.16			
0·00 BL, DC, SD, G, H	0·00 V, N	3·33	3·33	0·00	10·25			
0·00 BL; 10.00 DC; 18·75 SD; 8·05 G; 30·77 H	20·00 (14·29 V; 20·00 N)	46·15	69·22	76·91	192·3			
0·00 BL, DC, SD, G, H	0·00 V, N	0·00	0·00	0·00	0·00			

Adverse drug reactions are expressed as a percentage of the total number of subjects. *(A) aspirin, (B) bromfenac, (C) codeine, (D) diclofenac, (F) fenprofen, (I) ibuprofen, (K) ketoprofen, (M) meclofenamate, (N) naproxen, (P) paracetamol, (S) sulindac. †(M) more, (L) less effective than comparator; (E) equiactive, (N) No effect, (ADR) adverse drug reaction. ‡(BL) blood loss, (H) heartburn, (DC) diarrhoea/constipation, (SD) discomfort, (G) general. ‡(N) nausea, (V) vomiting. **'tid' — three times daily; 'qid' — four times daily. †† indicates that no adverse drug reactions were mentioned. ‡‡Clinical trials. §§n ≥ 40.

added peripheral anti-inflammatory activity with ibuprofen in conferring pain relief, a well-known property of NSAIDs (Rainsford 1996a, b).

These analyses of published reports of adverse events for ibuprofen and paracetamol taken at recommended OTC doses for < 7 days show that there are no statistically significant differences in the reports of adverse events in any of the major organ systems, irrespective of the type of adverse event reported or the overall frequency. In particular, there were no reports of melaena or haemorrhage from the gastrointestinal tract with ibuprofen in any of the published data. It is also apparent that the events reported were all minor, reversible upon cessation of drug therapy, and could be managed by the patient. No deaths were recorded and no hospitalization or major medical emergency treatment was necessary. These data attest to considerable safety for the public with both these drugs when taken alone.

Published reports of adverse events in subjects who have taken prescription doses of the drugs again reveal relatively high safety margins for both drugs. The incidence and types of adverse event reported in the major organ systems are identical with the two drugs. It is also apparent that ibuprofen, unlike other NSAIDs, has a relatively high margin of safety in the gastrointestinal and renal systems, and this is even more favourable in subjects who have received OTC doses of this drug (Rainsford & Quadir 1995; Moore et al 1996).

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