(44) Hurley, L. H., Chandler, C., Garner, T., Petrusek, R. L., Zimmer, S. (1979) J. Biol. Chem. 254, 605–608.
(45) Petrusek, R. L., Uhlenhopp, E., Duteau, N., Hurley, L. H. (1982) J. Biol. Chem. 257, 6207–6216.
(46) Lee, D. E., Okorodudu, A. O., Lambert, W. C., Lambert, M. W. (1982) Biochem. Biophys. Res. Commun. 107, 395–402.
(47) Hannan, M. A., Hurley, L. H. (1978) J. Antibiot. 31, 601–603.
(48) Hannan, M. A., Nasim, A. (1978) Mutation Res. 53, 309–316.
(49) Zbinden, G. (1964) in Plattner, Chemotherapy of Cancer, Proceedings of International Symposium Lugano, pp. 303–310, Elsevier, Amsterdam, London, New York.
(50) Myers, C. E., McGuire, W. P., Liss, R. H., Ifrim, I., Grotzinger, K., Young, R. C. (1977) Science 197, 165–167.
(51) Goodman, J., Hochstein, P., (1977) Biochim. Biophys. Res. Comm. 77, 797–803.
(52) Lubawy, W. C., Dallam, R. A., Hurley, L. H. (1980) J. Natl. Cancer Inst. 64, 105–109.
(53) Lubawy, W. C., Whaley, J., Hurley, L. H. (1979) Res. Comm. Chem. Pathol. Pharmacol. 24, 401–404.
(54) Lubawy, W. C., Hurley, L. H. (1981) in Biomedical and Clinical Aspects of Co-enzyme Q. Vol. 3. (Folkers, K., Yamamuro, Y. eds.), pp. 145–155, Elsevier/North-Holland Biomedical Press.
(55) Martin, D. G., Biles, C., Gerpheide, S. A., Hanka, L. J., Krueger, W. C., McGovern, J. P., Mizsak, S. A., Neill, G. L., Stewart, J. C., Visser, J. (1981) J. Antibiot. 34, 1119–1125.
(56) Swenson, D. H., Li, L. H., Hurley, L. H., Rokem, S., Petzold, G. L., Dayton, B. D., Wallace, T. L., Lin, A. H., Krueger, W. C. (1982) Cancer Res. 42, 2821-2828.
(57) Kaplan, D. J., Hurley, L. H. (1981) Biochemistry 20, 7572–7580.
(58) Hashimoto, Y., Shudo, K., Okamato, T. (1982) Tet. Lett. 23, 677–680.
(59) Kaplan, D. J., Tomasz, M. (1982) Biochemistry 21, 3006–3013.
(60) Hurley, L. H. (1980) Acc. Chem. Res. 13, 263–269.

Drug Interactions Through Binding to Cytochrome P 450: The Experience with H_2-Receptor Blocking Agents[3]

Ulrich Klotz[1, 2] and Ingrid W. Reimann[1]

Abstract: H_2-receptor blocking agents, such as cimetidine, ranitidine or oxmetidine, are consumed in large amounts often together with a variety of other drugs. There is increasing evidence that cimetidine interferes with the hepatic elimination of several drugs, thereby aggravating the effects of the comedication. Microsomal studies in vitro revealed that cimetidine binds in therapeutic concentrations to cytochrome P 450, which may represent the primary mechanism for its ability to inhibit drug metabolism and thereby interact with other drugs. The structurally different ranitidine (replacement of the imidazole in cimetidine by a furan ring) is about five times as potent as a H_2-receptor blocker and displays low affinity for binding sites on cytochrome P 450. Therefore, therapeutic doses of ranitidine do not impair the metabolism of other drugs. Preliminary data with oxmetidine suggest that it too does not interfere at the level of hepatic elimination. Thus, it is concluded that new therapeutic agents should be tested for their ability to bind to cytochrome P 450 to determine possible risks of drug interactions.

H_2-receptor blocking agents are among the most widely used drugs. They decrease basal and stimulated acid secretion (1, 2) and are effective drugs in the treatment of peptic ulcer (for review see 3, 4). In the Western world this disease afflicts approximately 12 % of the adult population, and about 1 % of total costs for all diseases are spent for peptic ulcer treatment (5). Thus, many patients will be taking H_2-blockers over prolonged periods. Hence, the potential of drug interactions exists and needs to be investigated.

H_2-blockers elevate the pH of the gastric juice to values between 3 and 5. Consequently, the absorption (bioavailability) of other drugs might be modified (for review see 6). Cimetidine and ranitidine are partly excreted unchanged by tubular secretion. Therefore, competition for this active transport process with endogenous creatinine (7) or other basic drugs (8) can also result in interactions. However, the prolongation of hexobarbital sleeping time in rats (9) and the clinical aggravation of warfarin action by cimetidine (10–12) have stimulated the most attention to interactions with H_2-blockers.

Cimetidine was released to the European market at the end of 1976 (USA: August 1977) followed by ranitidine 5 years later. Oxmetidine is still under clinical investigation. Since the initial reports on drug interactions with cimetidine (9, 12, 13) a

Table I. Inhibition of Hepatic Elimination of Different Drugs by Cimetidine.

Drug	References
Warfarin	12
Acenocoumarol	12
Phenandion	12
Phenytoin	36, 37, 38
Carbamazepine	39
Diazepam	40, 41, 42
Desmethyldiazepam	21
Chlordiazepoxide	43, 44
Alprazolam	45
Triazolam	45
Theophylline	46, 47, 48, 49, 50, 63
Coffeine	51, 52
Propranolol	29, 53, 54
Labetalol	55
Metoprolol	56
Penbutolol	57
Lidocaine	58, 64
Chlormethiazole	59
Imipramine	60, 81
Ethanol	61, 62

[1] Dr. Margarete Fischer-Bosch-Institut für Klinische Pharmakologie, Auerbachstr. 112, D-7000 Stuttgart 50
[2] To whom correspondence should be addressed.
[3] Supported by the Robert Bosch Foundation Stuttgart, Germany.

large number of papers have appeared. Table 1 summarizes all the drugs which are reported to be affected in their metabolism by cimetidine. As we will point out later, it is possible to circumvent these interactions with the selection of alternative drug treatments.

Possible Mechanism of Hepatic Interaction

a. Cytochrome P 450 Binding Experiments

In vitro experiments have revealed that cimetidine interacts with rat liver microsomes (14). Recorded difference spectra indicate that cimetidine binds to the ferrihemoprotein with a dissociation constant K_s of 70 μM. Therefore competition for binding sites between cimetidine and other ligands or drugs could result in the inhibition of mono-oxygenation reactions (14). A later report revealed that ranitidine had a much lower affinity (K_s = 1400–2800 μM) for cytochrome P 450 (15). In a similar study with suspensions of rat liver microsomes cimetidine produced a type II spectral change and showed a high affinity (K_s = 31 μM) for cytochrome P 450, while no spectral change indicative of drug binding to cytochrome P 450 was observed with ranitidine up to concentrations of 284 μM (16). Similar results were published by Speeg et al. (17) who failed to detect spectral changes with ranitidine in concentrations below 500 μM. The calculated dissociation constant of ranitidine was > 20000 μM, while cimetidine (K_{S1} = 13 μM, K_{S2} = 127 μM) was strongly bound to cytochrome P 450. Its metabolite, cimetidine sulfoxide, demonstrated only a low affinity (K_s = 1280 μM). Recent equilibrium partition studies with rat liver microsomes justify two distinct and independent classes of cytochrome P 450 sites capable of binding cimetidine with dissociation constants of 8.3 and 100 μM (18). These experimental binding studies clearly demonstrated that cimetidine can inhibit the cytochrome P 450 system in clinically relevant concentrations.

An important structural difference between these two H_2-blockers consists of the replacement of the imidazole ring of cimetidine with the furan ring of ranitidine. Since it was shown that substituted imidazoles can act as inhibitors of microsomal oxidation (18, 19), it might be concluded that the imidazole ring of cimetidine is responsible for the binding. However, oxmetidine (Fig. 1) which does not interact with the hepatic elimination of diazepam, theophylline and antipyrine (20), and

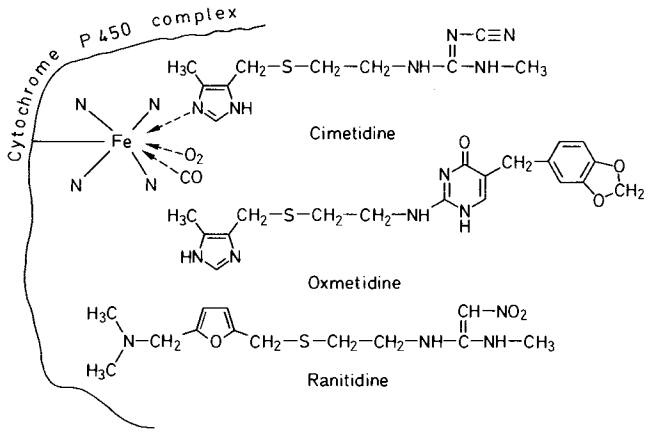

Fig. 1 Chemical structures of the H_2-receptor blocking agents cimetidine, ranitidine and oxmetidine, and the presumed site of attachment of cimetidine to cytochrome P 450.

cimetidine sulfoxide which has only a low affinity for cytochrome P 450 also possess an imidazole ring. Therefore, the side chain of the molecule can modify the binding characteristics of the substituted imidazoles. Other explanations of cimetidine's inhibitory potency (21) include contributions from yet unidentified reactive metabolite(s). In a recent abstract it was reported that rat liver cytochrome P 450 content and metabolism of 7-ethoxycoumarin decreased in a time dependent manner after preincubation with cimetidine. It was concluded that a reactive intermediate of cimetidine is produced during the preincubation which inactivates cytochrome P 450 (22).

b. Metabolic Studies

Several studies with rat liver microsomes have demonstrated an inhibition of drug metabolism by cimetidine: the apparent K_i-values were between 1 and 10 mM for aminopyrine N-demethylation (9, 23) and benzo(a)pyrene hydroxylation (24). Aryl hydrocarbon hydroxylase was inhibited between 50 and 90 %, if microsomes were prepared 2 hours after administration of 150 mg/kg (ip) cimetidine (25). Using an 18500 g (postmitochondrial) supernatant and 105000 g microsomal preparation, aminopyrine N-demethylase was inhibited by cimetidine (K_i = 0.55 mM and 0.13 mM, respectively) much more effectively than by ranitidine (K_i = 4 mM and 3.7 mM, respectively) or cimetidine sulfoxide (K_i = 3.5 mM and 4.4 mM). The tested H_2-antihistamines displayed mixed inhibition in all cases (17). Similar results were found with other substrates: Cimetidine competitively inhibited meperidine demethylation (290–1470 μM cimetidine) and pentobarbital hydroxylation (59 μM and 590 μM cimetidine); no effect of ranitidine on both reactions was seen at a concentration of 2.86 mM. Neither cimetidine (2.94 mM) nor ranitidine (2.86 mM) had an effect on microsomal glucuronidation of morphine (16).

In human liver biopsy samples cimetidine inhibited hydroxylation of benzo(a)pyrene with an IC_{50} of 1 mM, whereas for 7-ethoxycoumarin O-deethylase the IC_{50} was approximately 10 mM (26). Another comparative study demonstrated competitive inhibition of meperidine (pethidine) demethylation and non-competitive or mixed inhibition of pentobarbital hydroxylation by cimetidine (2.94 mM), but no inhibition of the metabolism of either substrate by 2.86 mM ranitidine (16). In addition the antipyrine clearance (32.5 ± 9.0 ml/h) was greatly reduced in the isolated perfused rat liver in the presence of cimetidine (10.1 ± 0.8 ml/h and 5.8 ± 1.5 ml/h after 1 and 5 mg doses,respectively). By contrast, neither ranitidine nor oxmetidine significantly altered antipyrine pharmacokinetics (27). These metabolic studies demonstrate that in comparable concentrations cimetidine but not ranitidine inhibits drug metabolism reactions where cytochrome P 450 is involved.

c. Pharmacodynamic Animal Models

Since the inhibition of hepatic P 450 activity should result in elevated or prolonged levels of many drugs administered concurrently with cimetidine, pharmacodynamic effects should be more pronounced. In fact, hexobarbital sleeping time is significantly prolonged (9, 23, 25), the anticoagulant effect of warfarin is potentiated (23), and there is significant increase in zoxazolamine paralysis time (23).

d. Pharmacokinetic Considerations

According to the equation hepatic clearance (CL_H) = liver

blood flow (Q)x hepatic extraction ratio (E) and dependent on the relative magnitude of CL_H to Q, a drug's CL_H can be characterized either as perfusion-dependent or capacity-limited (for review see 28). The already mentioned inhibition of drug metabolism by cimetidine results in a decrease in E and consequently of CL_H. There is considerable discussion if H_2-blocking agents reduce also hepatic perfusion. Indirect measurements of Q by the indocyanine green method suggest that both cimetidine and ranitidine might reduce Q by about 20 to 30 % (29, 30). However, this finding has been questioned for several theoretical and experimental reasons (31–34).

The elimination half-life ($t_{1/2}$), rather than the clearance, is often used to characterize the hepatic elimination of a drug. This is only valid, if the disposition of a drug (e. g. antipyrine) can be described by the one compartment open model, in which the $t_{1/2}$ is unaffected by the drug's distribution throughout the body (35). Numerous pharmacokinetic studies have been performed in man where calculations of CL and/or $t_{1/2}$ have been used to demonstrate the inhibitory potency of H_2-blocking agents.

Pharmacokinetic Investigations in Man

The hepatic elimination of a steadily increasing number of drugs (including the model compound antipyrine – for review see 6, 76, 77) is shown to be inhibited by cimetidine (Table 1), but not by ranidine (Table II a). In all of these metabolic reactions the mixed function oxygenase which includes cytochrome P 450 (or P 448) is involved (phase I reactions). This functional impairment by cimetidine is documented either by a decrease in CL and a prolongation of $t_{1/2}$ or by an increase in the monitored drug levels. In contrast, glucuronidation of drugs (phase II reaction which is independent of the cytochrome P 450 system) is not affected by cimetidine (Table II b). There seems to be no tolerance or decrease over time in the inhibition of drug metabolism by cimetidine, and these interactions develop rapidly within one day of pre-treatment with therapeutic doses (17, 21, 40). Following withdrawal of cimetidine recovery of oxidative drug metabolism occurs within 48 hours (17, 44, 63).

Table II A: The Hepatic Elimination of Drugs is not Impaired by Ranitidine.

Drug	References
Warfarin	65
Phenytoin	66
Diazepam	67, 68
Theophylline	69
Lidocaine	70
Propranolol	68, 71
Antipyrine (phenazone)	69, 72
Aminopyrine (aminophenazone)	72
Ethanol	62

Table II B: Glucuronidation of Drugs is not Inhibited by Cimetidine.

Drug	References
Oxazepam	21, 73
Lorazepam	73
Temazepam	82
Morphine	74
Phenprocoumon	75

Clinical and Practical Consequences

If the elimination of a drug is impaired by co-administration of a second drug, elevated plasma levels for a prolonged period of time will result from this interaction. Therefore drugs whose therapeutic or toxic effects are correlated with their plasma concentrations should be reduced in their dosage. In any case, multi-drug treatment should be guided by careful monitoring of the clinical performance of the patient and the pharmacodynamic and pharmacokinetic parameters of each drug.

For any new compound such interactions should be evaluated during drug development by the described approaches. Binding to cytochrome P 450, effects on metabolic reactions in vitro, and pharmacokinetic/pharmacodynamic experiments in animals could provide strong indications for such drug interactions in man. As we have learned from the investigations with H_2-blocking agents, the results of these pre-clinical studies can be cautiously extrapolated to the clinical situation. Thus, the safety of new drug treatments might improve. Based on the results of such studies, particularly where information on mechanisms underlying drug interactions is learned, alternative treatments may be suggested. If a new compound interacts with drugs that are eliminated by phase I reactions, one could select a substance for concomitant therapy which is eliminated by the renal route (if shown to be unaffected!) or by phase II metabolic reactions. On the other hand, it is possible to modify the chemical structure such that the inhibitory effects on cytochrome P 450 are lost, while therapeutic efficacy is retained (example ranitidine and oxmetidine).

The inhibitory potency of cimetidine on cytochrome P 450 reactions suggests a new indication for its therapeutic use. Cimetidine has been shown in animal studies to reduce effectively the hepatotoxicity of acetaminophen which is caused by a reactive intermediate metabolite generated by cytochrome P 450 (78, 79). However, the clinical value of cimetidine as an antidote that prevents toxic metabolite formation and could be used together with or replace N-acetylcysteine, remains to be established.

In conclusion, the story of the drug-drug interactions involving H_2-receptor blocking agents has contributed some valuable lessons for future drug development.

References

(1) Domschke, W., Lux, G., Domschke, S. (1980) Gastroenterology 79, 1267–1271.
(2) Sewing, K.-Fr., Billian, A., Malchow, H. (1980) Gut 21, 750–752.
(3) Brogden, R. N., Heel, R. C., Speight, T. M., Avery, G. S., (1978) Drugs 15, 93–131.
(4) Brogden, R. N., Carmine, A., Heel, R. C., Speight, T. M., Avery, G. S. (1982) Drugs 24, 267–303.
(5) Bodemar, G., Gotthard, R., Ström, M., Walan, A., Jönsson, B., Bjarulf, P. (1980) in Further Experience with H_2-Receptor Antagonists in Peptic Ulcer Disease and Progress in Histamine Research (Torsoli et al., ed.) Excerpta Medica, Amsterdam, pp. 59–67.
(6) Somogyi, A., Gugler, R. (1982) Clin. Pharmacokin. 7, 23–41.
(7) Dubb, J. W., Stote, R. M., Familiar, R. G., Lee, K., Alexander, F. (1978) Clin. Pharmacol. Ther. 24, 76–83.

(8) Somogyi, A., McLean, A., Heinzow, B. (1983) Eur. J. Clin. Pharmacol. 25, 339–345.
(9) Puurunen J., Pelkonen, O. (1979) Eur. J. Pharmacol. 55, 335–336.
(10) Silver, B. A., Bell, W. R. (1979) Ann. Int. Med. 90, 348–349.
(11) Wallin, B. A., Jacknowitz, A., Raich, P. C. (1979) Ann. Int. Med. 90, 993.
(12) Serlin, M. J., Sibeon, R. G., Mossmann, S., Breckenridge, A. M., Williams, J. R. B., Atwood, J. L., Willoughby, J. M. T. (1979) Lancet 2, 317–319.
(13) Klotz, U., Anttila, V.-J., Reimann, I. (1979) Lancet 2, 699.
(14) Rendić, S., Šunjić, V., Toso, R., Kajfež, F., Ruf, H. H. (1979) Xenobiotica 9, 555–564.
(15) Rendić, S., Alebić-Kolbah, T., Kajfež, F., Ruf, H.-H. (1982) Xenobiotica 12, 9–17.
(16) Knodell, R. G., Holtzmann, J. L., Crankshaw, D. L., Steele, N. M., Stanley, L. N., (1982) Gastroenterology 82, 84–88.
(17) Speeg Jr., K. V., Patwardhan, R. V., Avant, G. R., Mitchell, D. C., Schenker, S., (1982) Gastroenterology 82, 89–96.
(18) Wilkinson, C. F., Hetnarzski, K., Hicks, L. J. (1974) Pesticide Biochem. Physiol. 4, 299–312.
(19) Tong, G. L., Lien, E. J. (1976) J. Pharm. Sci. 65, 1651–1654.
(20) Gugler, R., Klotz, U., Jensen, C., Somogyi, A., unpublished own observations.
(21) Klotz, U., Reimann, I., (1980) Eur. J. Clin. Pharmacol. 18, 517–520.
(22) Jensen, J. C., Gugler, R., (1983) Naunyn-Schmiedeberg's Arch. Pharmacol. 322, R 110 (abstract).
(23) Serlin, M. J., Challiner, M., Park, B. K., Turcan, P. A., Breckenridge, A. M., (1980) Biochem. Pharmacol. 29, 1971–1972.
(24) Pelkonen, O., Puurunen, J. (1980) Biochem. Pharmacol. 29, 3075–3080.
(25) Drew, R., Rowell, J., Grygiel (1981) Res. Commun. Chem. Pathol. Pharmacol. 33, 81–93.
(26) Puurunen, J., Sotaniemi, E., Pelkonen, O. (1980) Eur. J. Clin. Pharmacol. 18, 185–187.
(27) Mihaly, G. W., Smallwood, R. A., Anderson, J. D., Jones, D. B., Webster, L. K., Vajda, F. J. (1982) Hepatology 2, 828–831.
(28) Wilkinson, G. R. (1975) Ann. Rev. Pharmacol. 15, 11–27.
(29) Feely, J., Wilkinson, G. R., Wood, A. J. J. (1981) N. Engl. J. Med. 304, 392–396.
(30) Feely, J., Guy, E. (1982) Lancet I, 169.
(31) Jackson, E. J. (1981) N. Engl. Med. 305, 99–100.
(32) Lebrec, D., Goldfarb, G., Benhanon, J.-P. (1981) N. Engl. J. Med. 305, 100.
(33) Grainger, S. L., Marigold, J. H., Keeling, P. W. N. (1982) Lancet I, 398.
(34) Klotz, U., Baughmann Jr., R. A., Massoud, N., Williams, R. L., Benet, L. Z. (1983) Verhandl. Dtsch. Inn. Med. 89, 634–635.
(35) Riegelman, S., Loo, J. C. K., Rowland, M. (1968) J. Pharm. Sci. 57, 117–123.
(36) Neuvonen, P. J., Tokola, R. A., Kaste, M. (1981) Eur. J. Clin. Pharmacol. 21, 215–220.
(37) Algozzine, G. J., Stewart, R. B., Springer, P. K. (1981) Ann. Intern. Med. 95, 244–245.
(38) Hetzel, D. J., Bochner, F., Hallpike, J. F., Shearman, D. J. C., Hann, C. S. (1981) Br. Med. J. 282, 1512.
(39) Telerman-Toppet, N., Duret, M. E., Coers, C. (1981) Ann. Intern. Med. 94, 544.
(40) Klotz, U., Reimann, I. (1980) N. Engl. J. Med. 302, 1012–1014.
(41) Klotz, U., Reimann, I. (1981) Clin. Pharmacol. Ther. 30, 513–517.
(42) Gough, P. A., Curry, S. H., Araujo, O. E., Robinson, J. D., Dallman, J. J. (1982) Brit. J. Clin. Pharmacol. 14, 739–742.
(43) Desmond, P. V., Patwardhan, R. V., Schenker, S., Speeg Jr., K. V. (1980) Ann. Intern. Med. 93, 266–268.
(44) Patwardhan, R. V., Johnson, R. F., Sinclair, A. P., Schenker, S., Speeg Jr., K. V. (1981) Gastroenterology 81, 547–551.
(45) Greenblatt, D. J., Abernethy, D. R., Divoll, R. B., Smith, R. B., Shader, R. I. (1983) Clin. Pharmacol. Ther. 33, C 16 (abstract).
(46) Campbell, M. A., Plachetka, J. R., Jackson, E., Moon, J. F., Finley, P. R. (1981) Ann. Intern. Med. 95, 68–69.
(47) Jackson, J. E., Powell, J. R., Wandell, M., Bentley, J., Dorr, R., (1981) Am. Rev. Respir. Dis. 123, 615–617.
(48) Reitberg, D. P., Bernhard, H., Schentag, J. J., (1981) Ann. Intern. Med. 95, 582–585.
(49) Roberts, R. K., Grice, J., Wood, L., Petroff, V., McGuffie, C. (1981) Gastroenterology 81, 19–21.
(50) Weinberger, M. M., Smith, G., Milavetz, G., Hendeles, L. (1981) N. Engl. J. Med. 304, 672.
(51) Broughton, H. J., Rogers, H. J. (1981) Brit. J. Clin. Pharmacol. 12, 155–159.
(52) May, D. C., Jarboe, C. H., van Bakel, A. B., Williams, W. M. (1982) Clin. Pharmacol. Ther. 31, 656–661.
(53) Heagarty, A. M., Donovan, M. A., Castleden, C. M., Pohl, J. F., Patel, L., Hedges, A. (1981) Br. Med. J. 282, 1917–1919.
(54) Reimann, I. W., Klotz, U., Siems, B., Frölich, J. C. (1981) Br. J. Clin. Pharmacol.12, 785–790.
(55) Daneshmend, T. K., Roberts, C. J. C. (1981) Lancet 1, 565.
(56) Kirch, W., Köhler, H., Spahn, H., Mutschler, E. (1981) Lancet 2, 531–532.
(57) Spahn, H., Kirch W., Mutschler, E. (1983) Br. J. Clin. Pharmacol. 15, 500–501.
(58) Feely, J., Wilkinson,G. R., McAllister, C. B., Wood, A. J. J. (1982) Ann. Intern. Med. 96, 592–594.
(59) Shaw, R. G., Bury, R. W., Mashford, M. L., Breen, K. J., Desmond, P. V. (1981) Eur. Clin. Pharmacol. 21, 83–85.
(60) Abernethy, D. R., Greenblatt, D. J., Shader, R. I. (1983) Clin. Pharmacol. Ther. 33, 237 (abstract).
(61) Feely, J., Wood, A. J. J. (1982) JAMA 247, 2819–2821.
(62) Seitz, H. K., Bösche, J., Czygan, P., Veith, S., Simon, B., Kommerell, B. (1983) Lancet 1, 760.
(63) Vestal, R. E., Thummel, K. E., Musser, B., Mercer, G. D. (1983) Br. J. Clin. Pharmacol. 15, 411–418.
(64) Knapp, A. B., Maguire, W., Keren, G., Karmen A., Levitt, B., Muira, D. S., Somberg, J. C. (1983) Ann. Intern. Med. 98, 174–177.
(65) Serlin, M. J., Sibeon, R. G., Breckenridge, A. M. (1981) Br. J. Clin. Pharmacol. 12, 791–794.
(66) Watts, R. W., Hetzel, D. J., Bochner, F., Hallpike, J. F., Hann, C. S., Shearman, D. J. C. (1983) Br. J. Clin. Pharmacol. 15, 499–500.
(67) Klotz, U., Reimann, I. W., Ohnhaus, E. E. (1983) Eur. J. Clin. Pharmacol. 24, 357–360.
(68) Klotz, U., Reimann, I. W. (1981) in The Clinical Use of Ranitidine, The Medicine Publishing Foundation, Oxford, U. K., pp. 97–103.
(69) Breen, K. J., Bury, R., Desmond, P. V., Mashford, M. L., Morphett, B., Westhood, B., Shaw, R. G. (1982) Clin. Pharmacol. Ther. 31, 297–300.
(70) Feely, J., Guy, E. (1983) Br. J. Clin. Pharmacol.15, 378–379.
(71) Reimann, I. W., Klotz, U., Frölich, J. C. (1982) Clin. Pharmacol. Ther. 32, 749–757.
(72) Henry, D. A., Mc Donald, I. A., Kitchingman, G., Bell, G. D., Langman, M. J. S. (1980) Br. Med. J. 281, 775–777.
(73) Patwardhan, R. V., Yarborough, G. W., Desmond, P. V., Johnson, R. F., Schenker, S., Speeg Jr., K. V. (1980) Gastroenterology 79, 912–916.
(74) Mojaverian, P., Fedder, I. L., Vlasses, P. H., Rotmensch, H. H., Rocci Jr., M. L., Swanson, B. N., Ferguson, R. K. (1982) Br. J. Clin. Pharmacol. 14, 809–813.
(75) Harenberg, J., Steiger, Ch., de Vries, J. X., Walter, E., Weber, E., Zimmermann, R. (1982) Br. J. Clin. Pharmacol. 14, 292–293.
(76) Klotz, U., Reimann, I. W. (1983) Klin. Wschr. 61 625–632.
(77) Reimann, I. W., Klotz, U. (1983) Inn. Med. 10, 31–40.
(78) Mitchell, M. C., Schenker S., Avant, G. R., Speeg Jr., K. V. (1981) Gastroenterology 81, 1052–1060.
(79) Jackson, J. E. (1982) Life Sci. 31, 31–35.
(80) Reily, P. E. B., Carrington, L. E., Winzor, D. J. (1983) Biochem. Pharmacol. 32, 831–835.
(81) del Miller, D., Macklin, M. (1983) Am. J. Psychiatry 140, 351–352.
(82) Greenblatt, D. J., Divoll, M., Abernethy, D. R., Ochs, H. R., Shader, R. I. (1983) Clin. Pharmacokin. 8, 233–252.