J. Pharm. Pharmacol. 1981, 33: 61–62
Communicated July 28, 1980

0022–3573/81/010061–02 $02.50/0

Effect of paracetamol coadministration on aspirin-induced gastrointestinal bleeding in dogs

J. L. LEELING*, N. JOHNSON, JNR., R. J. HELMS, *Toxicology Department, Miles Laboratories, Inc., P.O. Box 40, Elkhart, Indiana 46515, U.S.A.*

Seegers et al (1978, 1979) report that coadministration of paracetamol and aspirin significantly inhibited the formation of gastric erosions in rats fasted for 36 h. However, rats being hypersecretors of gastric acid (Adashek & Grossman 1963) are highly susceptible to ulceration, especially during starvation. Thus, the rat may not be a suitable species with which to obtain preclinical data on the gastrointestinal (g.i.) toxicity of organic acids, such as aspirin. Phillips (1973) showed the dog to be a relevant species, responding to ingestion of plain aspirin in a manner similar to man (i.e., g.i. microbleeding and consequent occult faecal blood loss at doses near the therapeutic range). The study described was made to determine the effect of concurrent paracetamol administration on aspirin-induced g.i. toxicity in the dog.

Fifteen male beagles, 9·6–13·0 kg, not used in a faecal blood loss study for at least a year, were given a physical examination including a complete blood count before the study began. Each dog, caged individually with free access to food and water, received intravenously 1·0 ml of 0·9% NaCl (saline) containing 50 μCi of $^{59}FeSO_4$ on study day minus 19. Since it has been established that aspirin-induced g.i. microbleeding is significantly reduced when buffered aspirin preparations are used (Leonards & Levy 1969, 1972), for maximum effect suspensions of regular aspirin were used. Dogs were assigned at random to the columns of three 5 × 5 latin squares. Five treatments were randomly assigned to rows within the squares. These treatments, administered orally (twice daily in complete crossover fashion), were: distilled water (2 ml kg^{-1}), 4% aqueous Tween 80 (suspending vehicle—2 ml kg^{-1}), aspirin suspension (62·5 mg kg^{-1}), paracetamol suspension (62·5 mg kg^{-1}), and a suspension containing aspirin and paracetamol (62·5 mg kg^{-1} of each).

Starting on day 1 alternating 5-day control (no dosing) and 7-day treatment periods were initiated which continued to day 60 when the 5th treatment period was terminated.

Microbleeding was determined by measurement, and comparison, of the ^{59}Fe content of 24 h stool collections and of weekly whole blood samples essentially as described by Phillips (1973). In the present study ^{59}Fe counted (Armac, Packard Instrument Co., Downers Grove, Illinois, U.S.A.) with about 8·3% efficiency with a background count rate of about 550 counts min^{-1}.

Average daily volumes of occult blood, observed in the faeces of 15 dogs during the 5 treatment periods are summarized in Table 1. Significant residual effects of treatments were not evidenced during control periods. Analysis of variance and multiple t-testing (Scheffe 1967) of these data revealed that those treatments which contained aspirin were statistically different from those which did not.

Table 1. Summary of average daily faecal blood loss.

Treatment*	Daily faecal blood loss (ml)**
Distilled water	0·39 ± 0·03
4% aqueous Tween-80	0·35 ± 0·01
Paracetamol (62·5 mg kg^{-1})	0·40 ± 0·01
Aspirin (62·5 mg kg^{-1})	4·81 ± 0·28
Aspirin (62·5 mg kg^{-1}) and Paracetamol (62·5 mg kg^{-1})	5·46 ± 0·38

* By gavage, twice daily.
** Mean ±s.e.m., n = 85 (7 treatment days × 15 dogs).

The results of this study indicate clearly that simultaneous administration of paracetamol and aspirin does not reduce aspirin-induced g.i. toxicity (manifested by occult blood loss in faeces) in dogs. These results appear to be opposed to those of Seegers et al (1978) obtained with rats. However, Seegers et al (1979) report that in the rat the incidence of aspirin-induced erosion foci (and, probably, of g.i. microbleeding), unlike the development of erosions per se, is unaffected by coadministration of paracetamol. Since g.i. microbleeding at doses in the therapeutic range is a widely recognized side effect of unbuffered aspirin in man and since dogs may respond to aspirin ingestion in a manner similar to man (Phillips 1973), these results suggest that paracetamol-aspirin combinations for human use may not provide any advantage, in a toxicologic sense, over plain aspirin alone.

The authors thank Dr. David J. Buddrus for his interest interest in and support of this work and Ms. Jan Reedus and Mr. Rick Minegar for technical assistance.

* Correspondence.

REFERENCES

Adashek, K., Grossman M. I., (1963) Proc. Soc. Exp. Biol. Med. 112: 629–631

Leonards, J. R., Levy, G. (1969) J. Pharm. Sci. 58: 1277–1279

Leonards, J. R., Levy, G. (1972) Arch. Int. Med. 129: 457–460

Phillips, B. M. (1973) Toxicol. Appl. Pharmacol. 24: 182–189

Scheffe, H. (1967) The Analysis of Variance, Wiley & Sons, New York. p 73

Seegers, A. J. M., Jager, L. P. Van Noordwijk, J. (1978) J. Pharm. Pharmacol. 30: 84–87

Seegers, A. J. M., Jager, L. P. Van Noordwijk, J. (1979) Ibid. 31: 840–848

J. Pharm. Pharmacol. 1981, 33: 62–63
Communicated October 3, 1980

0022–3573/81/010062–02 $02.50/0

QSAR with random biological data

R. B. BARLOW, *Dept. of Pharmacology, Medical School, University of Bristol, Bristol BS8 1TD, U.K.*

In 1962 Hansch et al suggested that biological activity might be quantitatively related to chemical properties by a modification of the Hammett equation:

$$\log \frac{1}{C} = k\pi + k'\pi^2 + \rho\sigma + k''$$

where C is the concentration of a compound producing a standard biological response, σ is the Hammett substituent constant, expressing effects on electron distribution, and π is a parameter expressing effects on lipophilicity and is calculated from the change in log-partition coefficient between n-octanol and water. Hansch et al obtained values of σ and π for the substituents in 20 phenoxyacetic acids, measured the concentrations of the compounds which produced a standard growth of *Avena* coleoptiles and used the method of least squares to calculate the coefficients ρ, k, k′ and k″. Some idea of the goodness of fit was provided by comparing the experimental values of log 1/C with those calculated from the corresponding values of σ and π.

Subsequently many biological results have been fitted to equations of this type in attempts to establish quantitative structure-activity relationships (QSAR). The success of the operation is usually judged from the correlation coefficient, r, and standard deviation, s (Hansch & Fujita 1964; Tute 1971). For example, Hansch & Fujita reported that the phenol coefficients (PC) for 35 compounds tested against *M. pyogenes* var. *aureus* could be fitted to the equation

$$\log PC = 0{\cdot}001\pi^2 + 0{\cdot}953\pi - 0{\cdot}210\sigma + 0{\cdot}134$$

with r = 0·977 and s = 0·230. The correlation coefficient should represent

$$\sqrt{\frac{\text{explained variation}}{\text{total variation}}}$$

(Spiegel 1972) and the standard deviation is derived from the variance unexplained by regression,

$$S(PC_{observed} - PC_{calculated})^2$$

Because there are four coefficients (ρ, k, k′ and k″) to be calculated it might be expected that at least with small numbers of results some degree of correlation is inevitable (with only four results it should be perfect). Further, the limitations of the sensitivity of the method for measuring biological activity may tend to yield numbers which favour some degree of correlation. With a test capable of assessing activity over a million-fold range, the values of log 1/C will lie within 6 units but there is often great uncertainty with very weak compounds as to what the figure should be—a totally inactive compound cannot be represented on a log scale. It is therefore likely that an analysis will be restricted to those compounds whose activity lies within the range in which the test is considered to give reliable estimates; often this is less than 6 units. A further bias may also be introduced by the limited choice of substituents studied. Ideally the values of π and σ should be randomly distributed but this is seldom achieved and it is common to find that with both these parameters there are more positive values than negative ones.

This note describes an attempt to obtain some idea of the extent to which these factors may contribute to a correlation by examining some published results and replacing the experimental values of log 1/C by random values lying in the same range. Calculations were made with a Commodore PET 2001 computer and the procedure for obtaining the least-squares fit is outlined elsewhere (Barlow 1980). Studies were made with the original results involving 20 phenoxyacetic acids (Hansch et al 1962), with those for the 35 phenols referred to above (Hansch & Fujita 1964), and with results from the same paper for the toxicity of 14 benzoic acids to mosquito larvae. In each instance the original values for π and σ for each compound were taken and the computer's random number generator (RND(1)) was used to provide an 'estimate' of the biological activity. This function produces numbers between 0 and 1 and in a test of 20 000 values the distribution was as follows: <0·1, 1968; <0·2 but