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Do gastric contents modify antidotal efficacy of oral activated charcoal?

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1 The effect of food on the antidotal efficacy of activated charcoal was studied in six healthy volunteers, who ingested aspirin 1000 mg, mexiletine 200 mg and tolfenamic acid 400 mg in a randomized cross-over study.

2 Activated charcoal 25 g, suspended in water, was administered 5 min or 60 min after the drugs were taken on an empty stomach or after a standard meal.

3 The serum concentrations and the cumulative excretion into urine of the drugs were followed for 48 h.

4 When the drugs were taken on an empty stomach, activated charcoal given 5 min or 60 min afterwards reduced the bioavailability of the drugs by 75–98% or 10–60%, respectively.

5 Food moderately weakened the effect of activated charcoal administered 5 min after the drugs, but when the charcoal was given 1 h later the effect was still practically the same, the reduction of absorption varying in both cases in the range of 45-85%. Thus the efficacy of charcoal given 60 min after the drugs was better after a standard meal than on an empty stomach.

6 Presence of food in the stomach of patients with drug overdosage modifies the efficacy of activated charcoal and gives it more time to adsorb drugs in the gastrointestinal canal, possibly by slowing gastric emptying rate.

Keywords activated charcoal drug absorption gastric contents

Introduction

Activated charcoal is a well known adsorbent whose ability to reduce the gastrointestinal absorption of different drugs has been shown in numerous studies as pointed out in some recent reviews (Hayden & Comstock, 1975; Neuvonen, 1982). The impairing effect of gastrointestinal contents on the adsorption capacity of activated charcoal has been known since the classical works of Andersen (1948). However, there is little quantitative information about the effect of food on the antidotal efficacy of charcoal in humans.

The aim of the present study was to compare the effect of oral activated charcoal on the gastrointestinal absorption of three test drugs, aspirin, mexiletine and tolfenamic acid. Charcoal was taken on an empty stomach or after a standard meal 5 min or 60 min after the drugs.

Methods

Six healthy volunteers, one male and five females, aged 21–26 years (weighing 53–70 kg), participated in the study. The results of physical examination before and after the study were normal. Written informed consent was obtained from each volunteer. The study protocol was accepted by the Local Ethical Committee. For the first 8 h after drug ingestion, the volunteers were under direct medical supervision in an outpatient clinic.

A randomized cross-over study design of six phases was used at intervals of 2 weeks. The drugs and doses used were: aspirin 1000 mg (Aspirin, Bayer, Leverkusen, Germany), mexiletine hydrochloride 200 mg (Mexitil, Boehringer Ingelheim, Ingelheim am Rhein, Germany) and tolfenamic acid 400 mg (Clotam, Medica Pharmaceutical Company Ltd, Hel-

sinki, Finland). Activated charcoal (Carbomix, Medica Pharmaceutical Company Ltd) was a specially granulated form of Norit A, which rapidly forms a homogenous suspension when shaken with water. The suspension was prepared just before use.

All three drugs (total three capsules and two tablets) were swallowed together with 100 ml of water at 08.00 h on an empty stomach or immediately after a standard meal consisting of meat balls weighing about 150 g and one roll with cheese. Activated charcoal 25 g suspended in 150 ml of water or water without charcoal was taken 5 min or 60 min after the drugs. Timed blood samples were taken 0, 1.5, 3, 5, 8, 24 and 48 h after drug ingestion. Serum was separated within 1 h and divided into three tubes, for determination of each drug. Urine was collected in fractions for 0–24 h and 24–48 h. The samples were stored at −20°C until analyzed.

Serum and urine concentrations of salicylate were measured fluorometrically (Chirigos & Udenfriend, 1959) and those of tolfenamic acid by high performance liquid chromatography (Pentikäinen *et al.*, 1981). The concentrations of mexiletine in serum and urine were determined by the electron capture gas-chromatographic method of Pachecus *et al.* (1982) using OV-225 column, and ephedrine as the internal standard. Toluene was used instead of diethyl ether and pentafluoropropionic anhydride instead of heptafluorobutyric anhydride.

The effect of charcoal on the absorption of the drugs was characterized by the area under the serum drug concentration-time curve from 0 to 48 h ($AUC_{0-48\ h}$) which was calculated by the trapezoidal rule. In addition, peak drug concentrations in serum (C_{max}), peak times (t_{max}), and the cumulative excretion of salicylates and mexiletine in urine over 0–48 h were calculated.

Friedman's two-way analysis of variance was used for the statistical analysis of the results and Duncan's multiple range test was applied to find the source of possible differences between all six phases (Duncan, 1955). The need for logarithmic transformation prior to the Duncan's test was judged by means of the method described by Bartlett (1937).

Results

Aspirin

Eating did not significantly modify the bioavailability of aspirin. However, C_{max} was somewhat lower and it was reached later than in the control group (Figures 1 & 2, Table 1).

When the drugs were taken on an empty stomach, activated charcoal administered 5 min afterwards reduced the absorption of aspirin by over 75%, based on the $AUC_{0-48\ h}$. Activated charcoal given 1 h after the drugs reduced the absorption of aspirin by only 25%.

Presence of food in the gastrointestinal canal weakened the effect of activated charcoal taken 5 min after the drugs, the $AUC_{0-48\ h}$ being about 45% of the control. When the adsorbent

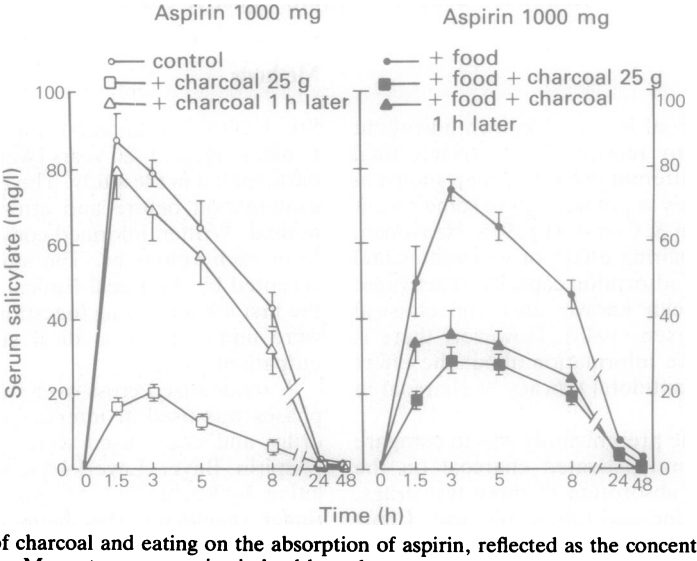

Figure 1 Effect of charcoal and eating on the absorption of aspirin, reflected as the concentration of salicylates in serum. Mean ± s.e. mean in six healthy volunteers.

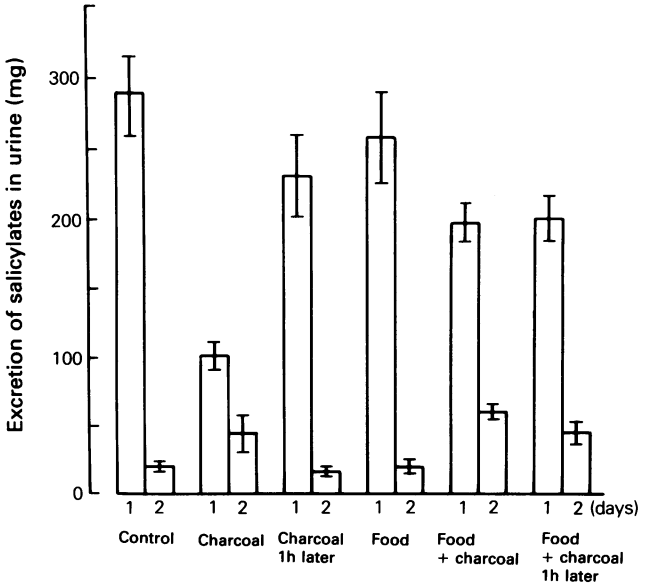

Figure 2 Effect of charcoal and eating on the absorption of aspirin, reflected as the cumulative excretion of salicylates into urine over 0–48 h. Mean ± s.e. mean in six healthy volunteers.

was administered 1 h after the ingestion of food and the drugs, its effect remained the same.

A rebound increase in the excretion of salicylate into urine was noticed during the second day after drug ingestion when activated charcoal had been administered 5 min after the drugs on an empty stomach. A similar rebound increase also occurred when charcoal was given 5 min or 1 h after a standard meal and the drugs.

Mexiletine

Administration of activated charcoal 5 min after the drugs, taken on an empty stomach, very effectively inhibited the absorption of mexiletine—the cumulative excretion of mexiletine into urine was about 3% and the $AUC_{0-48\ h}$ about 4% of the control, respectively (Figures 3 and 4, Table 1). When charcoal was given 60 min after the drugs, it had no significant effect on the absorption of mexiletine. However, when the drugs were taken after a standard meal the efficacy of activated charcoal was almost irrespective of whether the adsorbent was administered 5 min or 60 min after the drugs: the absorption of mexiletine was reduced by 80–90%.

Tolfenamic acid

Unlike aspirin the bioavailability of tolfenamic acid, based on the $AUC_{0-48\ h}$, was almost doubled when the drug was ingested with food. Likewise, C_{max} was slightly increased and it was reached later than in the control (Figure 5, Table 1). Because of its spare excretion into urine, urinary excretion data gave no reliable information about the absorption of tolfenamic acid.

Administration of charcoal on an empty stomach 5 min or 1 h after the drugs reduced the $AUC_{0-48\ h}$ by about 90% or 60%, respectively. When the drugs were taken after a standard meal the effect of activated charcoal 5 min after the drugs was poorer than in the control phase. However, as with other test drugs, the effect of charcoal remained the same even when it was administered 1 h after a standard meal and the drugs: the inhibition of tolfenamic acid absorption was about 50%, based on the $AUC_{0-48\ h}$.

Discussion

There is increasing evidence that oral activated charcoal may inhibit the gastrointestinal absorption of different drugs. Although the influence of gastrointestinal contents on the adsorptive capacity of charcoal *in vitro* has been recognized since Andersen (1948), almost all *in vivo* experiments have been done with fasting subjects or experimental animals.

Table 1 Effect of charcoal (25 g) and eating on the absorption of aspirin (1000 mg), mexiletine (200 mg) and tolfenamic acid (400 mg). All drugs were ingested together. Mean ± s.e. mean in six healthy volunteers

	t_{max}	C_{max}		$AUC_{0-48\ h}$		48 h excretion in urine	
	(h)	(mg/l)	(% of the control)	(mg l^{-1} h)	(% of the control)	(mg)	(% of the control)
Aspirin+charcoal (control)	1.5 ± 0.0	8.8 ± 5.9[b,e–f]	100	940 ± 74[b–c,e–f]	100	308 ± 26[b]	100
Aspirin+charcoal 25 g	3.0 ± 0.0	20.3 ± 2.1[a,c–d,f]	23	218 ± 29[a,c–f]	23	144 ± 12[a,c–f]	47
Aspirin+charcoal 1 h later	1.5 ± 0.0	79.9 ± 7.5[b,e–f]	91	701 ± 113[a–b,d–e]	75	246 ± 29[b]	80
Aspirin+food (control)	3.0 ± 0.0	74.4 ± 8.,6[b,e–f]	100	995 ± 81[b–c,e–f]	100	278 ± 34[b]	100
Aspirin+food+charcoal 25 g	3.3 ± 0.3	29.3 ± 3.0[a,c–d]	39	438 ± 34[a–d]	44	256 ± 20[b]	92
Aspirin+food+charcoal 1 h later	3.3 ± 1.0	39.5 ± 4.4[a–d]	53	503 ± 50[a–b,d]	51	245 ± 21[b]	88
Mexiletine+no charcoal (control)	1.5 ± 0.0	0.30 ± 0.02[b,e–f]	100	2.82 ± 0.37[b,e–f]	100	24.0 ± 5.4[b,e–f]	100
Mexiletine+charcoal 25 g	3.0 ± 0.8	0.02 ± 0.01[a,c–d,f]	7	0.10 ± 0.05[a,c–d,f]	4	0.79 ± 0.52[a,c–f]	3
Mexiletine+charcoal 1 h later	1.5 ± 0.0	0.32 ± 0.03[b,e–f]	107	2.66 ± 0.33[b,e–f]	94	22.3 ± 5.9[b,e–f]	93
Mexiletine+food (control)	4.5 ± 0.3	0.31 ± 0.04[b,e–f]	100	3.88 ± 0.55[b,e–f]	100	15.4 ± 2.9[b,e–f]	100
Mexiletine+food+charcoal 25 g	4.0 ± 0.9	0.04 ± 0.01[a,c–d,f]	13	0.20 ± 0.03[a,c–d,f]	5	1.88 ± 0.45[a–d]	12
Mexiletine+food+charcoal 1 h later	1.8 ± 0.3	0.12 ± 0.03[a–f]	39	0.64 ± 0.15[a–e]	16	2.60 ± 0.86[a–d]	17
Tolfenamic acid+no charcoal (control)	1.8 ± 0.3	3.18 ± 0.56[b]	100	18.6 ± 2.3[b–c]	100	–	–
Tolfenamic acid+charcoal 25 g	1.5 ± 0.0	0.65 ± 0.09[a,c–f]	20	2.29 ± 0.26[a,c–f]	12	–	–
Tolfenamic acid+charcoal 1 h later	1.5 ± 0.0	2.88 ± 0.78[b]	91	7.02 ± 2.08[a–b,d–f]	38	–	–
Tolenamic acid+food (control)	3.1 ± 0.5	3.82 ± 0.63[b]	100	29.8 ± 2.9[b–c,e–f]	100	–	–
Tolfenamic acid+food+charcoal 25 g	2.8 ± 0.5	3.28 ± 0.49[b]	86	16.1 ± 1.6[b–d]	54	–	–
Tolfenamic acid+food+charcoal	3.7 ± 0.4	2.32 ± 0.2[b]	61	15.4 ± 2.0[b–d]	52	–	–

a–f: significantly ($P < 0.05$) different from

drug+no charcoal[a]
drug+charcoal 25 g[b]
drug+charcoal 1 h later[c]
drug+food[d]
drug+food+charcoal 25 g[e]
drug+food+charcoal 1 h later[f]

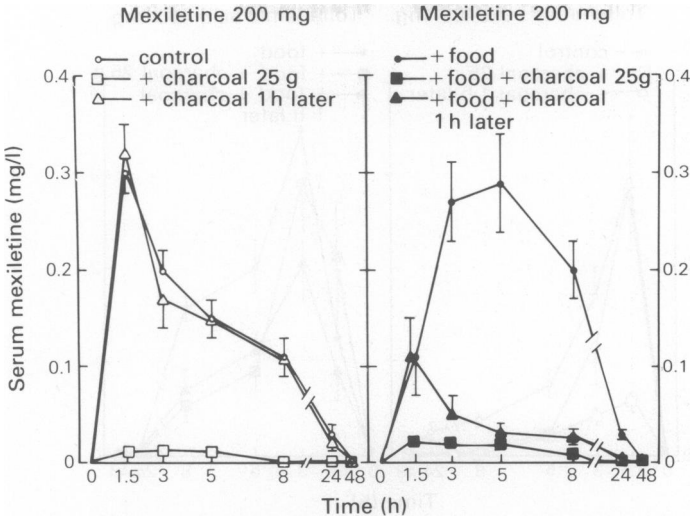

Figure 3 Effect of charcoal and eating on the absorption of mexiletine, reflected as the concentration of mexiletine in serum. Mean ± s.e. mean in six healthy volunteers.

The simultaneous presence of food, drugs and activated charcoal in the gastrointestinal canal is a challenge to try to understand the complex series of interactions involved in drug absorption. Different food components can have different effects, and food may interact in opposite ways, even with drugs that are chemically related (Melander, 1978). Therefore, the net effect of food and activated charcoal on drug bioavailability can be predicted only by direct human studies of the drug in question.

In man it has been demonstrated that food reduces the inhibiting effect of charcoal on aspirin absorption: the percentage of a 1 g aspirin dose recovered in the urine, when 10 g activated charcoal was given immediately after the aspirin, was about 60% for fasted subjects and 75% for subjects who had eaten a standard

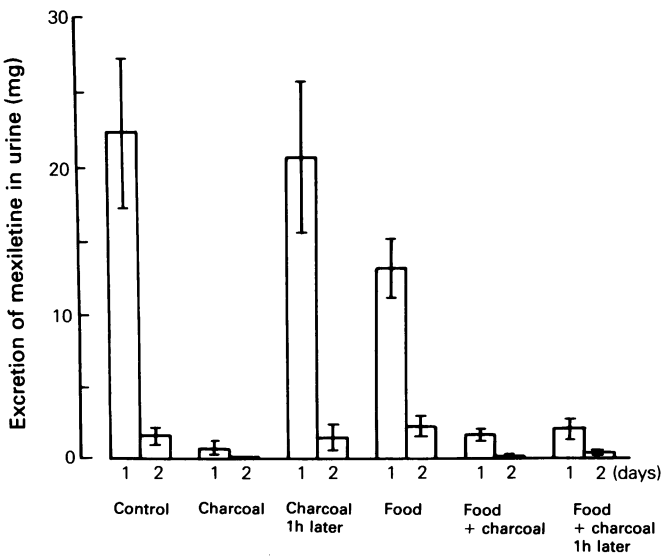

Figure 4 Effect of charcoal and eating on the absorption of mexiletine, reflected as the cumulative excretion of mexiletine into urine over 0–48 h. Mean ± s.e. mean in six healthy volunteers.

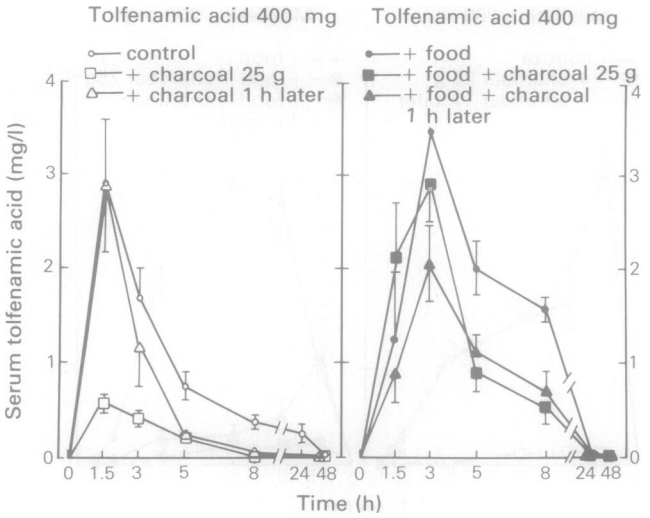

Figure 5 Effect of charcoal and eating on the absorption of tolfenamic acid, reflected as the concentration of tolfenamic acid in serum. Mean ± s.e. mean in six healthy volunteers.

breakfast 15 min prior to the test (Levy & Tsuchiya, 1972). In dogs, however, the opposite effect was observed when they had been fed 1 h before the test (Atkinson & Azarnoff, 1971). Theoretically, it can be expected that food would reduce the efficacy of antidotal charcoal by being a physical barrier between the drug and charcoal; food may also compete with the drug for the binding sites of charcoal, thus leading to diminished effectiveness of the antidote. On the other hand, food will no doubt slow down gastric motility thereby reducing the rate of drug absorption, which gives charcoal more time to adsorb the drug. The net result of these competing factors can be either an increased or a decreased bioavailability, depending on the person, the type and amount of food eaten, the time interval between food and charcoal administration and the pharmacological and chemical characteristics of the drug (Cooney, 1980).

In the present study all drugs (aspirin, mexiletine and tolfenamic acid) were ingested simultaneously to ensure comparable conditions for individual drugs. At least theoretically, the drugs themselves might have interacted. However, their absorption and elimination during the control phase corresponded well to that described in the literature (Levy & Tsuchiya, 1972; Pentikäinen *et al.*, 1981; Pachecus *et al.*, 1982). No side effects occurred during the study. Aspirin was chosen for the present study because it has been a generally used test drug in pharmacokinetic studies involving charcoal as a gastrointestinal adsorbent. Furthermore it is a common cause of poisoning in many countries: e.g. in England and Wales approximately 200 deaths due to salicylate poisoning among the adults occur each year (Meredith & Vale, 1981). Mexiletine is an antiarrhythmic agent with properties similar to those of lignocaine. In toxic doses it causes nausea, vomiting, severe CNS symptoms, e.g. confusion and convulsions. It has also a depressing effect on the cardiac muscle, and in overdoses it thus leads to severe arrhythmias with high mortality (Jequier *et al.*, 1976; Vale & Meredith, 1981). Tolfenamic acid, a new anti-inflammatory agent, has not been reported to have caused fatal intoxications. However, overdosage with closely related mefenamic acid has increased steadily over the past decade and it has caused severe epileptic convulsions but no reported deaths (Balali-Mood *et al.*, 1981).

The bioavailability of aspirin was unaffected by eating. However, peak drug concentrations in serum were slightly decreased and peak times increased in comparison to the control. These results fit well to previous results obtained with aspirin utilizing the same type of pharmaceutical formulation (Melander, 1977). The total absorption of mexiletine was not significantly altered when the drug was taken after a standard meal, but the bioavailability of tolfenamic acid was increased. Changes in t_{max} reflect the effect of food on gastric motility, since the rate of absorption of an orally administered agent is directly related to the rate at which drugs pass from the stomach to the intestine (Nimmo, 1979).

When the drugs were taken on an empty stomach, activated charcoal given immediately afterwards reduced their absorption very effectively. If the administration of the adsorbent was delayed for 60 min, the inhibiting effect of charcoal on drug absorption from an empty stomach was weakened by 40–95%; the great variation might be due to differences in dissolution characteristics of aspirin, mexiletine and tolfenamic acid. These results are in accordance with previous studies (Neuvonen *et al.*, 1978, 1983).

When the drugs were ingested after a standard meal the efficacy of activated charcoal administered 5 min afterwards was somewhat less than when both drugs and charcoal were taken on an empty stomach. Interestingly, the reduction of absorption remained unchanged, varying in the range of 45–85%, even though charcoal was delayed for 60 min – thus the efficacy of charcoal 60 min after the drugs was better after a standard meal than on an empty stomach. The present results demonstrate that food in the stomach of patients with drug overdosage modifies the efficacy of activated charcoal and gives it more time to adsorb drugs in the gastrointestinal canal, possibly by slowing gastric emptying rate.

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References

Andersen, A. H. (1948). Experimental studies on the pharmacology of activated charcoal. III. Adsorption from gastrointestinal contents. *Acta Pharmac.*, **4**, 275–284.

Atkinson, J. P. & Azarnoff, D. L. (1971). Comparison of charcoal and attapulgite as gastrointestinal sequestrants in acute drug ingestions. *Clin. Tox.*, **4**, 31–38.

Balali-Mood, M., Critchley, J. A. J. H., Proudfoot, A. T. & Prescott, L. F. (1981). Mefenamic acid overdosage. *Lancet*, **i**, 1354–1356.

Bartlett, M. S. (1937). Some examples of statistical methods of research in agriculture and applied biology. *J. Roy. Stat. Soc.* (Suppl.) **4**, 137–183.

Chirigos, M. A. & Udenfriend, S. (1959). A simple fluorometric procedure for determining salicylic acid in biologic tissues. *J. lab. clin. Med.*, **54**, 769–772.

Cooney, D. O. (1980). *Activated charcoal*, p. 50. New York and Basel: Marcel Dekker, Inc.

Duncan, D. B. (1955). Multiple range and multiple F tests. *Biometrics*, **11**, 1–42.

Hayden, J. W. & Comstock, E. G. (1975). Use of activated charcoal in acute poisoning. *Clin. Tox.*, **8**, 515–533.

Jequier, P., Jones, R. & Mackintosh, A. (1976). Fatal mexiletine overdose. *Lancet*, **i**, 429.

Levy, G. & Tsuchiya, T. (1972). Effect of activated charcoal on aspirin absorption in man. *Clin. Pharmac. Ther.*, **13**, 317–322.

Melander, A. (1978). Influence of food on the bioavailability of drugs. *Clin. Pharmacokin.*, **3**, 337–351.

Melander, A., Berlin-Wahlen, A., Bodin, N.-O., Danielson, H., Gustafsson, B., Lindgren, S. & Westerlund, D. (1977). Bioavailability of D-propoxyphene, acetyl salicylic acid, and phenazone in a combination tablet (Doleron): interindividual variation and influence of food intake. *Acta med. Scand.*, **202**, 119–124.

Meredith, T. J. & Vale, J. A. (1981). Salicylate poisoning. In *Poisoning: Diagnosis and Treatment*, eds Vale, J. A. & Meredith, T. J., pp 97–103. London, Dordrecht, Boston: Update Books.

Neuvonen, P. J. (1982). Clinical pharmacokinetics of oral activated charcoal in acute intoxications. *Clin. Pharmacokin.*, **7**, 465–489.

Neuvonen, P. J., Elfving, S. M. & Elonen, E. (1978). Reduction of absorption of digoxin, phenytoin and aspirin by activated charcoal in man. *Eur. J. clin. Pharmac.*, **13**, 213–218.

Neuvonen, P. J., Vartiainen, M. & Tokola, O. (1983). Comparison of activated charcoal and ipecac syrup in prevention of drug absorption. *Eur. J. clin. Pharmac.*, **24**, 557–562.

Nimmo, W. S. (1979). Gastric emptying and drug absorption. In *Drug Absorption*, eds Prescott, L. F. & Nimmo, W. S., pp. 11–20. Hong Kong: Adis Press.

Pachecus, A., Santoni, Y., Fornaris, M., Magnum, S., Aubert, C., Ragon, A. & Cano, J. P. (1982). Simultaneous plasma levels determination of mexiletine and one of its metabolites by electron capture gas-liquid chromatography. *Arzneimittelforsch.*, **32**, 688–693.

Pentikäinen, P. J., Neuvonen, P. J. & Backman, C. (1981). Human pharmacokinetics of tolfenamic acid, a new anti-inflammatory agent. *Eur. J. clin. Pharmac.*, **19**, 359–365.

Vale, J. A. & Meredith, T. J. (1981). Poisoning due to cardiovascular drugs. In *Poisoning: Diagnosis and Treatment*, eds Vale, J. A. & Meredith, T. J., pp. 117–122. London, Dordrecht, Boston: Update Books.

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