References

- Adams, P. C., Storey, G. C. A., Morley, A. R., Adams, D. M., Callaghan, J., Holt, D. W. & Campell, R. W. F. (1983). Amiodarone in tissue quantitative ultrastructural considerations. *Eur. Heart J.*, **4**, Suppl. E, 110.
- Moysey, J. O., Jaggarao, N. S. V., Grundy, E. N. & Chamberlain, D. A. (1981). Amiodarone increases plasma digoxin concentrations. *Br. med. J.*, **282**, 272.
- Serlin, M. J. & Sibeon, R. G. (1981). Dangers of amiodarone and anticoagulant treatment. *Br. med. J.*, **283**, 58.
- Tartini, R., Steinbrunn, W., Kappenberger, L. & Meyer, U. A. (1982). Dangerous interaction between amiodarone and quinidine. *Lancet*, **i**, 1327-1329.

Gastric aspiration by nasal intubation: an additional route of elimination for metronidazole

For most drugs and xenobiotics, the detoxification process is associated with liver metabolism or direct elimination by the kidney. In other cases, however, other routes of elimination have been described: biliary excretion, pulmonary elimination, intestinal metabolism, etc . . . In this letter, we would like to report another potentially important route of elimination for drugs which are administered to patients undergoing gastro-intestinal surgery.

In a previous study performed in 10 patients (Thiercelin *et al.*, 1984), metronidazole was given intravenously (for 3 days) and then orally (for 3 days) to all patients. The main pharmacokinetic finding was that after chronic administration and despite using the same dosage regimen, the area under the curves (AUC) at steady-state after the oral route exceeded the AUC at steady-state after the i.v. route in all cases (124.7 ± 6.7 vs 83.1 ± 4.6 mg/l.h).

This unexpected observation compared to what has been published in literature (Bergan *et al.*, 1981; Houghton *et al.*, 1979) prompted us to perform a complementary study in seven patients,

in which the oral administration was replaced by an intravenous infusion (for 3 days). In this situation there were no significant differences between AUCs which therefore ruled out an explanation based on the recovery from surgery of the patients.

One of the hypotheses suggested to explain the results was that clearances during i.v. and oral administration were not equal and that the continuous gastric aspirations which were performed during and after surgery, i.e. only during the i.v. sequences, played a major role in the elimination of the drug. To clarify this point, a specific study was carried out subsequently in which six patients were treated with i.v. metronidazole, 500 mg three times daily for 3 consecutive days. H.p.l.c. assay (Diquet *et al.*, 1980) was used to quantify metronidazole in the gastric secretion. The total amount of drug recovered in the last 24 h of gastric aspiration is shown in Table 1. An approximation of the extra dose required to replace losses due to gastric aspiration can be made from these data. The recommendation of a daily infusion of 180 mg

Table 1 The total amount of drug recovered in the last 24 h of gastric aspiration

Patients	Gastric aspirate			
	Volume (l)	Metronidazole concentration (mg/l)	Total amount of drug (mg)	% of daily dose
PA	0.7	193	135	9.0
VI	1.6	214	342	22.8
ME	0.6	123	174	4.9
PO	1.0	165	165	11.0
CA	0.3	100	30	2.0
BE	0.7	233	163	10.8

extra metronidazole per litre of aspirate would give a fairly accurate replacement rate for each of the six individuals.

During or after gastro-intestinal surgery it is a classical procedure to give nutrients and drugs by the parenteral route, and to continuously remove the gastric secretions from the stomach by nasal intubation. If a drug concentrates in this liquid, its removal could be considered as an additional clearance. Gastric juice contains only the unbound fraction of the drug. The above mentioned results would fit with the pharmacokinetic features of metronidazole (San von Deker *et al.*, 1975): large volume of distribution, low binding to plasma protein, small molecule, extensive diffusion rate. This additional route of elimination could be important for some drugs extensively used by anaesthetists during gastro-

intestinal interventions, as well as in other types of surgery where gastric aspiration is undertaken. Thus, for all molecules with a rapid diffusion rate which are only weakly bound to protein, it is important to measure the proportion of the drug 'cleared' from the body through the nasal tubing. If this is not done clinical care may be compromised.

B. DIQUET, J. F. THIERCELIN & P. SIMON

Département de Pharmacologie, Clinique, CHU Pitié-Salpêtrière, Paris, France

F. GHESQUIÈRE & P. VIARS

Département d'Anesthésiologie et de Réanimation, CHU Pitié, Salpêtrière, Paris, France

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References

- Bergan, T., Bjerke, P. E. M. & Farsa, O. (1981). Pharmacokinetics of metronidazole in patients with enteric disease compared to normal volunteers. *Chemotherapy*, **27**, 233–238.
- Diquet, B., Colin, J. N. & Singlas, E. (1980). Dosage plasmatique du metronidazole par C.L.H.P. *Ann. Biol. Clin.*, **38**, 223–225.
- Houghton, G. W., Thorne, P. S., Smith, J., Templeton, R. & Collier, J. (1979). Comparison of the pharmacokinetics of metronidazole in women volunteers following either a single oral or i.v. dose. *Br. J. clin. Pharmacol.*, **8**, 337–341.
- San von Deker, D. R., Chien, Y. W., Lin, T. K. & Lambert, M. J. (1975). Binding of metronidazole and its derivatives to plasma proteins: an assessment of drug binding phenomenon. *J. pharm. Sci.*, **61**, 1797–1803.
- Thiercelin, J. F., Diquet, B., Lévêque, C., Ghesquière, F., Simon, P. & Viars, P. (1984). Pharmacokinetics and bioavailability of metronidazole in patients undergoing gastro-intestinal surgery. *Clin. Pharmac. Ther.* (in press).