EAKINS, K. E., KARIM, S. M. M. & MILLER, J. D. (1970). *Ibid.*, **39**, 556–563.
FERREIRA, S. H., MONCADA, S. & VANE, J. R. (1973). *Ibid.*, **49**, 86–97.
MCGIFF, J. C. (1975). *Life Sci.*, **16**, 805.
MCGIFF, J. C., TERRAGNO, N. A., MALIK, K. U. & LONIGRO, A. J. (1972). *Circ. Res.*, **31**, 36–43.
MONCADA, S., FERREIRA, S. H. & VANE, J. R. (1972). Abstr. Vth Int. Congress Pharmac. San Francisco, 160.
PALMER, M. A., PIPER, P. J. & VANE, J. R. (1973). *Br. J. Pharmac.*, **49**, 226–242.
VANE, J. R. (1971). *Nature New Biol.*, **231**, 232–235.
VANE, J. R. & FERREIRA, S. H. (1975). *Life Sci.*, **16**, 804.

Passage of intravenously administered pethidine into gastric juice in man

T. GESSNER, R. TRUDNOWSKI, R. RICO, J. REMPEL, *Roswell Park Memorial Institute, New York State Department of Health, 666 Elm Street, Buffalo, New York 14203, U.S.A.*

Pethidine is eliminated in animals and man mainly after biotransformation to metabolites which are excreted in urine (Burns, Berger & others 1955; Plotnikoff, Elliott & Way, 1952; Plotnikoff, Way & Elliott, 1956). In their studies of tissue distribution of the ^{14}C label following parenteral administration of [^{14}C]pethidine to rats, Plotnikoff & others (1952) noted significant amounts of radioactivity in the gastrointestinal tract. They concluded "The radioactive material in all probability represents metabolic products of the parent compound." We wish to report that irrespective of any possible excretion of metabolites of pethidine via bile and/or gastrointestinal tract, pethidine itself can appear in the tract after parenteral administration by passing into the gastric juice. The process also involves concentration of the drug to levels one to two orders of magnitude greater than those in plasma.

We studied four patients who received pethidine potentiated nitrous oxide-oxygen anaesthesia. Preoperative medication was 10 mg of diazepam. The amount of pethidine each patient received in divided doses ranged from 225 to 600 mg (i.v.). Curare was the relaxant drug in doses from 15 to 22 mg. Gastric samples along with simultaneous blood samples were obtained before and from 10 min up to 4 h after the last dose of pethidine. All samples were analysed for pethidine by gas chromato-

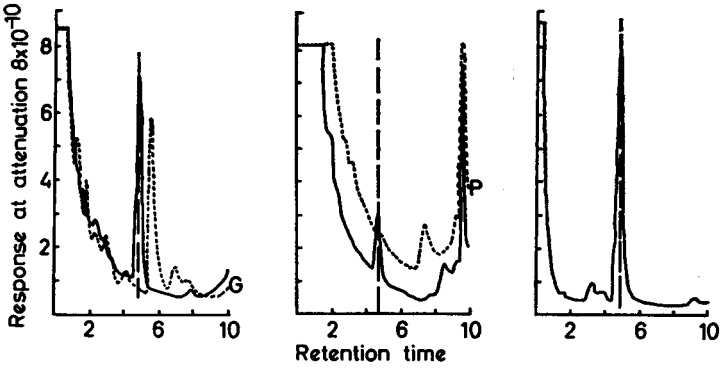

FIG. 1. Identification of pethidine in gastric juice and plasma of a patient administered pethidine intravenously. Left panel: gas chromatograms of extracts of gastric juice; broken line—zero time sample, i.e. before administration of pethidine; solid line–sample taken 75 min after administration of pethidine. Right panel: gas chromatogram of authentic pethidine sample. Middle panel: gas chromatograms of extracts of plasma; broken line–zero time sample; solid line–sample taken 75 min after administration of pethidine.

graphy on a glass column packed with 3% OV-17 on 100–120 mesh Gas-Chrom Q, according to Goehl & Davison (1973).

All gastric juice samples of the patients treated with pethidine contained the drug at concentrations substantially higher than those found in plasma samples taken concurrently. Typically, the plasma and gastric juice of an untreated patient did not appear to contain any compound which behaved like pethidine on gas chromatography (see Fig. 1, zero time samples depicted by broken lines). After administration of pethidine, g.l.c. of gastric juice extract revealed the presence of a peak which coincided with that of authentic pethidine standard (Fig. 1). Plasma samples taken concurrently also contained such a peak. The gastric juice concentrations ranged from 22 to 300 μg ml^{-1}. The ratio of drug concentration in gastric juice to that in plasma ranged between 7 and 430.

These results indicate that the drug not only readily passes from plasma through gastric mucosa, but also becomes sequestered and concentrated in gastric juice. We believe this is due to ion trapping. Shore, Brodie & Hogben (1957) and Brodie & Hogben (1957), observed that gastric mucosa appears to behave like a lipid membrane allowing passage of the lipid soluble form (unionized) of a compound. They reported that when basic compounds such as aniline or quinine were infused into dogs, these accumulated in gastric juice to concentrations 40 times higher than those found in plasma.

Pethidine is a basic compound with a pKa of 8·7. In gastric juice at pH 1, it should be almost completely ionized, whereas, in plasma (pH 7·4) about 57% of the plasma pethidine would be ionized (taking into account about 40% protein binding). The plasma/gastric juice pH gradient allows the ionized form of pethidine to be more concentrated in the juice than in plasma, i.e., be ion trapped on the gastric juice side (see Fig. 2). A theoretically possible concentration gradient can be calculated to be of the order of 10^6. It is not surprising, therefore, that we have observed concentration ratios as high as 400.

To our knowledge, our report is the first evidence of pethidine trapping in gastric juice in man. It appears likely that the phenomenon is applicable not only to pethidine but to many other basic drugs, and that it may contribute to the prolonged stay of such drugs in the body.

It is not uncommon to observe in the post-anaesthetic period that patients treated with pethidine have periods of awakening and falling asleep. Moreover, one of our

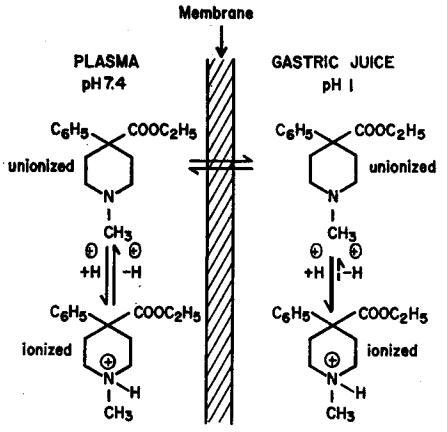

FIG. 2. Partition of the unionized and ionized form of pethidine on both sides of the lipid membrane of gastric mucosa. This illustrates passage across the membrane of the lipid soluble unionized form, and trapping of the ionized form of the drug.

patients showed an increase in plasma pethidine accompanied by a fall in gastric concentration of the drug. This suggests that the gastric juice acts as a depot for the drug, the pethidine being initially trapped in the juice, and then after it passes into the small intestine with the gastric contents, reaction with the alkaline intestinal contents promotes its reabsorption into the plasma.

It is noteworthy that foetal intoxication with such local anaesthetics as lignocaine and mepivacaine has been associated with the presence of high concentrations of these anaesthetics in gastric contents of the foetuses (Sunshine & Fike, 1964; Sinclair, Fox & others, 1965; Datta, Houle & Fox, 1975).

Thanks are due to Mr. James Ewing and Miss Alice MacDonald for their excellent technical assistance. This work was supported in part by USPHS Grants CA-14729 and CA-13038.

March 4, 1975

REFERENCES

BRODIE, B. B. & HOGBEN, C. A. M. (1957). *J. Pharm. Pharmac.*, **9**, 345–380.

BURNS, J. J., BERGER, B. L., LIEF, P. A., WALLACE, A., PAPPER, E. M. & BRODIE, B. B. (1955). *J. Pharmac. exp. Ther.*, **114**, 289–298.

DATTA, S., HOULE, G. L. & FOX, G. S. (1975). *Canad. Anaesth. Soc. J.*, **22**, 79–83.

GOEHL, T. J. & DAVISON, C. J. (1973). *J. pharm. Sci.*, **62**, 907–909.

PLOTNIKOFF, N. P., ELLIOTT, H. W. & WAY, E. L. (1952). *J. Pharmac. exp. Ther.*, **104**, 377–386.

PLOTNIKOFF, N. P., WAY, E. L. & ELLIOTT, H. W. (1956). *Ibid.*, **117**, 414–419.

SHORE, P. A., BRODIE, B. B. & HOGBEN, C. A. (1957). *Ibid.*, **119**, 361–369.

SINCLAIR, J. C., FOX, H. A., LENTZ, J. F., FULD, G. L. & MURPHY, J. (1965). *New Engl. J. Med.*, **273**, 1173–1177.

SUNSHINE, I. & FIKE, W. W. (1964). *Ibid.*, **271**, 487–490.

Comparative potencies of European and Indian squill

F. S. HAKIM, N. G. BOWERY, F. J. EVANS, *Departments of Pharmacognosy and Pharmacology, The School of Pharmacy, 29/39 Brunswick Square, London WC1N 1AX, U.K.*

Squill B.P.C. 1973 is defined as the bulb of *Urginea maritima* L. Baker (Fam. Liliaceae), the European or white squill. In the November issue of the *Pharmaceutical Journal* (1974) it was proposed that Squill B.P.C. could be substituted by its common adulterant Indian squill (*Urginea indica* Kunth.). The limited phytochemical work available (Seshadri & Subramanian, 1950; Rangaswami & Subramanian, 1954, 1955; Krishna Rao & Rangaswami, 1967) concerning Indian squill, suggests that the bufadienolide glycosides are different in their detailed structure from those of European squill. The problem is further aggravated by reports (Seshadri & Subramanian, 1950; Chopra, Chopra & others, 1958) that commercial samples of Indian squill are mixtures of *Urginea indica* Kunth. and *Scilla indica* Roxb. and most phytochemical investigations are based upon a mixture of the two species. Squill glycosides are said to possess a reflex expectorant action in low doses (B.P.C. 1973) and they are constituents of some cough mixtures. Since patients on cardiac glycosides could also be exposed to Indian squill in such preparations, we have considered it advisable to compare the cardiotoxic potencies of European and Indian squill.