MECHANISM FOR GASTRIC ACCUMULATION OF MEPERIDINE AND EFFECT OF ANTACID

R.J. TRUDNOWSKI AND T. GESSNER

ABSTRACT

The effect of hydrogen ion activity (pH) on the degree of meperidine sequestration in gastric contents was studied in 15 patients. Those patients with higher gastric juice cH^+ (lower pH) showed greater accumulation with time. At a cH^+ more than 10,000 nmol/l, (pH < 5) concentration usually reached 100 μg/ml within the 60-minute period after administration of 200 mg of meperidine. When cH^+ was less than 100 nmol/l (pH > 7) gastric concentrations remained low, being only slightly greater than those of plasma. Oral administration of antacid may be a practical method for preventing sequestration of meperidine in gastric juice.

WE HAVE PREVIOUSLY REPORTED[1-3] that meperidine accumulated rapidly in gastric juice after intravenous administration. Gastric concentrations often reached levels up to 100 times those in plasma. One possible explanation for the accumulation is the phenomenon of ion trapping. Meperidine with a pK of 8.7 ionizes more in solutions of lower pH. Unionized meperidine readily crosses gastric mucosa into the stomach, where it ionizes and cannot return across the membrane.

If this were the chief reason for gastric accumulation of meperidine it should be possible to reduce it by manipulation of cH^+. We have tested this hypothesis in a small group of patients to determine whether it is possible to diminish meperidine sequestration by antacid treatment.

METHODS AND PROCEDURES

Patients included in the study were those receiving meperidine-potentiated nitrous oxide-oxygen anaesthesia for operations to treat malignant tumors or their sequellae. The study was explained to them and they consented to be subjects.

Preoperative medication was diazepam 5-10 mg and scopolamine 0.4 mg. We inserted a nasogastric sump and took a gastric juice sample before any meperdine was administered. A meperidine-free venous blood sample was also taken at the time when the peripheral intravenous line was established.

We administered 30 ml of a magnesium and aluminum hydroxide suspension through the tube to alternate patients, washing it into the stomach with 30 ml of isotonic saline. The other patients received 60 ml of isotonic saline through the sump.

Intravenous meperidine and diazepam provided the neurolept anaesthetic induction. A local anaesthetic spray of the mouth, throat, and larynx facilitated tracheal intubation. Maintenance anaesthesia consisted of nitrous oxide with oxygen supplemented by meperidine, with curare as the muscle relaxant. Gastric samples for measurement of cH^+ (pH) and meperidine were taken 30 minutes and one hour after the first dose of meperidine, and at the end of operation. Accompanying venous blood samples were taken from the arm opposite to that which received the intravenous meperidine.

RESULTS

Seven men and eight women between the ages of 22 and 75 years were subjects in the study. Their average weight was 75.1 kg. ASA physical status was either 2 or 3. Duration of operation was between one and four hours. Plasma concentrations of meperidine varied between 1.0 and 3.0 μg/ml while the cH^+ of the blood samples ranged between 47.64 and 45.18 nmol/l (pH 7.322–7.345).

Table I shows the gastric meperidine levels of those patients who received no alkali. In general, for similar time periods and doses of meperidine, more gastric meperidine accumulates as cH^+ increases (pH becomes lower). The apparent exception, patient J.B., was influenced by other factors. She underwent a splenectomy with extensive gastric manipulation resulting in gastric wall oedema. This increased the resistance to diffusion of the drug. But even here, gastric con-

R.J. Trudnowski, M.D., Chief, Department of Anesthesiology. T. Gessner, Ph.D., Associate Cancer Research Scientist, Department of Experimental Therapeutics. Roswell Park Memorial Institute, New York State Department of Health, 666 Elm Street, Buffalo, New York, 14263, U.S.A.

This work was supported in part by United States Public Health Service Grants CA-13038 and CA-14729.

TABLE I

GASTRIC SECRETION OF MEPERIDINE

				After meperidine					
		Pretreatment		30 minutes		60 minutes		End of operation	
Patient	Sex	pH	Meperidine μg/ml	pH	Meperidine μg/ml	pH	Meperidine μg/ml	pH	Meperidine μg/ml
J.B.	F	2.50	0	2.70	20.71	2.50	74.10	1.80	134.75
		*31.63×10^5	(0)	*19.95×10^5	(100)	*31.63×10^5	(200)	*15.84×10^6	(300)
V.B.	M	6.80	0	5.35	26.90	4.80	148.59	5.30	119.41
		*158.40	(0)	*44.67×10^2	(200)	*15.84×10^3	(300)	*50.12×10^2	(300)
B.C.	F	6.30	0	6.08	8.54	5.98	32.36	5.98	32.36
		*591.20	(0)	*831.70	(200)	*10.47×10^2	(200)	*10.47×10^2	(200)
C.C.	F	7.20	0	6.50	0	6.20	1.21	6.30	107.80
		*63.10	(0)	*316.30	(100)	*631.00	(150)	*591.20	(200)
D.G.	M	6.42	0	6.50	25.64	5.70	31.27	2.30	106.02
		*380.20	(0)	*316.30	(200)	*19.95×10^2	(200)	*59.12×10^5	(200)
P.K.	M	6.40	0	5.95	15.05	5.22	42.62	5.22	42.62
		*398.10	(0)	*11.12×10^2	(200)	*60.25×10^2	(200)	*60.25×10^2	(200)
J.V.	F	4.20	0	3.75	48.01	3.30	234.64	5.20	154.74
		*63.10×10^3	(0)	*17.79×10^4	(150)	*50.12×10^4	(250)	*63.10×10^2	(250)

( ) Cumulative total meperidine administered in mg.

*$[H^+]$ in mmol/l.

TABLE II

EFFECT OF ALKALI ON GASTRIC SECRETION OF MEPERIDINE

				After alkali and meperidine					
		Pretreatment		30 minutes		60 minutes		End of operation	
Patient	Sex	pH	Meperidine µg/ml	pH	Meperidine µg/ml	pH	Meperidine µg/ml	pH	Meperidine µg/ml
S.A.	M	3.50	0	7.84	2.67	7.16	4.05	7.16	40.05
		*31.63×10^4	(0)	*14.45	(150)	*69.19	(400)	*69.19	(400)
L.C.	F	4.50	0	7.40	0	7.35	0	7.10	0.23
		*31.62×10^3	(0)	*39.81	(150)	*44.67	(300)	*79.43	(400)
R.D.	M	2.90	0	7.10	14.00	6.90	88.45	6.70	98.10
		*12.56×10^5	(0)	*79.43	(200)	*125.60	(300)	*199.50	(800)
G.K.	F	6.83	0	7.08	1.45	7.08	1.90	7.72	2.50
		*147.90	(0)	*83.16	(150)	*83.17	(150)	*19.05	(150)
A.M.	M	1.30	0	4.70	42.28	4.90	115.58	5.10	122.34
		*50.12×10^6	(0)	*19.95×10^3	(150)	*12.55×10^3	(225)	*79.43×10^2	(650)
H.M.	F	6.40	0	7.28	2.29	7.41	3.94	7.62	4.21
		*398.10	(0)	*52.48	(200)	*38.91	(200)	*23.98	(200)
D.P.	M	1.15	0	7.30	0.60	6.28	63.99	6.10	86.92
		*70.80×10^6	(0)	*59.12	(250)	*524.80	(300)	*794.30	(300)
M.W.	F	6.32	0	7.68	0	7.40	5.00	6.60	30.31
		*478.70	(0)	*20.89	(100)	*39.81	(100)	*251.20	(100)

( ) Cumulative total meperidine administered in mg.

*$[H^+]$ in nmol/l.

centrations were well above plasma concentrations.

Table II shows the effect of alkali on the acidity of gastric contents and secretion of meperidine. The results are the same as those in Table I: as cH^+ falls (pH rises) gastric accumulation of meperidine falls. Patients whose gastric cH^+ could not be reduced to 100 nmol/l (pH raised to 7.0) accumulated significant amounts of meperidine in the stomach. On the other hand, if the gastric juice cH^+ was reduced to between 59.12 and 39.81 nmol/l (pH increased to 7.3–7.4) little or no accumulation occurred.

Discussion

Gastric drug sequestration can have a number of consequences. If the accumulation is large, the dose of drug given can be less effective than expected. On the other hand, the reabsorption which occurs after the gastric acid is neutralized by the alkaline intestinal contents may release sufficient narcotic to cause respiratory depression. Our data in previous studies show that five per cent of the drug administered is usually sequestered in gastric juice. However, a recent study of the narcotic fentanyl indicates the percentage is much greater if the gastric tissue itself is considered.[4] Analysis of sections of stomach wall showed that 16–20 per cent of the dose administered was present there. Reabsorption of this quantity of drug could cause the secondary respiratory depression previously described for fentanyl.[5] Similar findings can be expected for meperidine and other narcotics.

This study provides evidence for the ion trapping concept as an explanation for sequestration of meperidine in gastric juice following intravenous administration. At high cH^+ (low pH) values, when there was more ionization, large concentrations of drug were detected in the stomach. The concentration process was suppressed when the cH^+ (pH) gradient between plasma and gastric juice was abolished.

The administration of alkali may be a practical method of preventing sequestration of drug in the stomach, if this is desired. It would allow more drug to reach target organs and avoid the rebound effects from reabsorption of drug from the stomach and intestine.

References

1. Gessner, T., Trudnowski, R., Rico, R., Hobika, G. & Rempel, J. Accumulation of parenterally administered meperidine in gastric juice. Fed. Proc. *34*: 712 (1975).
2. Gessner, T., Trudnowski, R., Rico, R. & Rempel, J. Passage of intravenously administered pethidine into gastric juice in man. J. Pharm. Pharmacol. *28*: 79–81 (1976).
3. Trudnowski, R. & Gessner, T. Gastric excretion of intravenously administered meperidine in surgical patients. Anesth. and Analg. *58*: 88–92 (1979).
4. Stoeckel, H., Hengstmann, J. & Schüttler, J. Pharmacokinetics of fentanyl as a possible explanation for recurrence of respiratory depression. Brit. J. Anaesth. *51*: 741–745 (1979).
5. Becker, L., Paulson, B., Miller, R., Severinghaus, J. & Eger, E. Biphasic respiratory depression after fentanyl-droperidol or fentanyl alone to supplement nitrous oxide anesthesia. Anesthesiology *44*: 291–296 (1976).

Résumé

L'effet de la concentration en ion hydrogène (pH) sur la séquestration de la mépéridine dans le contenu gastrique a été étudié chez quinze patients. Une plus grande accumulation a été trouvée chez les patients dont la concentration gastrique en ions H^+ était plus élevée (pH abaissé). Lorsque la concentration en H^+ était plus grande que 10,000 nmol/l (pH 5), l'accumulation de narcotique atteignait ordinairement 100 µg/l en decà de 60 minutes après l'administration d'une dose de 200 mg de mépéridine. Lorsque concentration de narcotique dans le liquide gastrique est demeurée basse, à peine plus élevée que dans le plasma. L'administration orale d'antiacide peut s'avérer une méthode pratique pour prévenir la séquestration de la mépéridine dans le contenu gastrique.