- monomethylated tricyclic antidepressants during treatment with imipramine-like compounds. *Life Sci.*, **6**, 1895–1903.
- HAMMER, W., MARTENS, S. & SJÖQVIST, F. (1969). A comparative study of the metabolism of desmethylinipramine, nortriptyline and oxyphenylbutazone in man. *Clin. Pharmac. Ther.*, **10**, 44–49.
- MAHGOUB, A., IDLE, J.R., DRING, L.G., LANCASTER, R. & SMITH, R.L. (1977). Polymorphic hydroxylation of debrisoquine in man. *Lancet*, **ii**, 584–586.
- MELLSTRÖM, B., BERTILSSON, L., SÄWE, J., SCHULZ, H.-U. & SJÖQVIST, F. (1981). E- and Z-10-hydroxylation of nortriptyline: Relationship to polymorphic debrisoquine hydroxylation. *Clin. Pharmac. Ther.*, **30**, 189–193.
- POTTER, W.Z., BERTILSSON, L. & SJÖQVIST, F. (1981). Clinical pharmacokinetics of psychotropic drugs: Fundamental and practical aspects. In *Handbook of Biological Psychiatry*, VI, eds van Praag, H., Lader, M.H., Rafaelsen, O.J. & Sachar, E.J., pp 71–134. New York: Marcel Dekker Inc.
- POTTER, W.Z., CALIL, H.M., SUTFIN, T.A., ZAVADIL, A.P., JUSKO, W.J., RAPOPORT, J. & GOODWIN, F.K. (1982). Active metabolites of imipramine and desipramine in man. *Clin. Pharmac. Ther.*, **31**, 393–401.

NO SIGNIFICANT EFFECT OF METOCLOPRAMIDE ON MISONIDAZOLE ELIMINATION IN MAN

Misonidazole (Ro 07-0582) potentiates the effects of ionizing radiation on hypoxic tumour cells. Clinical studies of the drug at high doses have been limited by the risk of neurological toxicity in the form of peripheral neuropathy and less frequently convulsions (Dische *et al.*, 1977). Adverse effects have been shown to correlate with total tissue exposure to the drug as estimated by the area under the plasma concentration-time curve (AUC) (Dische *et al.*, 1977; Saunders *et al.*, 1978). Studies have shown that the elimination half-life ($t_{1/2}$) and consequently the AUC may be reduced by pretreating volunteers with enzyme inducing agents such as phenytoin and phenobarbitone which increase the rate of formation of the metabolite, *o*-desmethylnisonidazole (Williams *et al.*, 1983; Workman, 1979; Workman *et al.*, 1980).

Metoclopramide is likely to be used concurrently with misonidazole for its antiemetic activity during radiotherapy. Metoclopramide increases gastric motility and decreases small bowel transit time. This could potentially lead to higher and earlier peak plasma concentrations of misonidazole and possibly decreased AUC. In this study we have investigated the effect of metoclopramide administration on the pharmacokinetics of misonidazole elimination.

The study was carried out in six healthy volunteers (three male and three female) aged 20 to 25 years with weights ranging from 50 kg to 93 kg. Informed consent was obtained from each subject and the protocol was approved by the Hospital and University Ethics Committees. Each subject was considered normal based on a full physical examination, and haematological and biochemical screens. None of the subjects was on any regular medications.

Misonidazole elimination kinetics were studied before and after a 1 week course of metoclopramide. Each subject initially received an oral dose of misonidazole (1.0 g/m²) taken with water (200 ml). Venous blood samples were collected in EDTA tubes

at approximately 0, 0.25, 0.50, 0.75, 1, 2, 3, 4, 6, 8, 12, 14, 24, 36, and 48 h after misonidazole administration. The specimens were centrifuged immediately after collection and the plasma separated and stored frozen at –20°C. Misonidazole and *o*-desmethylnisonidazole were assayed by high performance liquid chromatography (Williams *et al.*, 1983). At least 1 week was allowed following the misonidazole dose prior to commencement of metoclopramide.

Metoclopramide (10 mg) was given orally 3 times daily with meals and at night for 9 days. On the eighth day each subject received a dose of misonidazole (1 g/m²) concurrently with the morning metoclopramide dose and venous blood samples collected as before.

A typical plasma concentration-time profile for misonidazole and desmethylnisonidazole before and after treatment with metoclopramide is shown in Figure 1. The effect of metoclopramide on the mean parameters is shown in Table 1. There was no significant difference between any of the mean parameters. However, a marked difference was observed in one subject. Prior to metoclopramide, this subject had a peak misonidazole concentration of 49 µg/ml after 0.5 h. His peak concentration after treatment was 27 µg/ml and this occurred at 8.0 h. There was also a 31% increase in terminal elimination half-life of misonidazole associated with a 22% decrease in clearance, a 32% increase in AUC for misonidazole and a 14% decrease in the AUC for desmethylnisonidazole, following metoclopramide administration.

One subject experienced an adverse reaction which was probably drug related and was consequently withdrawn before completing the trial. She was given the initial dose of misonidazole (1700 mg) and took metoclopramide for 1 week with no untoward effects. However, 2 h after administration of the second dose of misonidazole and the scheduled dose of metoclopramide (10 mg), she reported feeling nauseated and faint. She was examined and found to have a

Figure 1 Plasma concentrations of misonidazole (squares) and desmethylmisonidazole (circles) before (open) and after (closed) the administration of metoclopramide

sinus bradycardia of 44 beats/min. The blood pressure was unchanged. Blood samples were collected for a further 1.5 h but the study was abandoned when her second daily dose of metoclopramide was due. The subject gradually recovered with no residual effects. The beginning of the period of nausea and faintness corresponded with the peak misonidazole concentration of 46 $\mu\text{g/ml}$, a value, however, very similar to that observed following the first dose (43 $\mu\text{g/ml}$) when no adverse effects occurred. Pharmacokinetic parameters determined following the first dose were not unusual.

These adverse effects may have been related to a pharmacodynamic interaction between misonidazole and metoclopramide.

It is concluded that there is no significant phar-

macokinetic interaction between metoclopramide and misonidazole. The difference observed in the one subject is unexplained.

Some caution is necessary in extrapolating this data to debilitated patients with cancer.

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Table 1 The effect of metoclopramide on the pharmacokinetic elimination parameters for misonidazole

Parameter	Before metoclopramide	After metoclopramide
$t_{1/2}$ (h)	11.7 ± 0.7	12.4 ± 1.0
$V_{d\beta}$ (l)	37.3 ± 3.2	37.1 ± 2.9
CL (ml/min)	37.0 ± 2.6	35.2 ± 2.7
$\text{AUC}_{0-\infty} \text{Mis}^\dagger$ ($\mu\text{g ml}^{-1} \text{h}$)	779 ± 50	830 ± 62
$\text{AUC}_{0-48 \text{ h}} \text{Des}^\ddagger$ ($\mu\text{g ml}^{-1} \text{h}$)	83.2 ± 5.8	83.7 ± 8.2
Peak concentration ($\mu\text{g ml}^{-1}$)	44.6 ± 3.7	41.0 ± 4.2
Time to peak (h)	2.4 ± 0.6	4.0 ± 1.1

All values expressed as mean $\pm$ s.e. mean

[†]Misonidazole, [‡]desmethylmisonidazole

References

- DISCHE, S., SAUNDERS, M.I., LEE, M.E., ADAMS, G.W. & FLOCKHART, I.R. (1977). Clinical testing of the radiosensitizer Ro 07-0582: experience with multiple doses. *Br. J. Cancer*, **35**, 567-579.
- SAUNDERS, M.I., DISCHE, S., ANDERSON, P. & FLOCKHART, I.R. (1978). The neurotoxicity of misonidazole and its relationship to dose, half-life and concentration in the serum. *Br. J. Cancer*, **37**, 268-270.
- WILLIAMS, K.M., BEGG, E.J., WADE, D.N. & O'SHEA, K. (1983). The effects of phenytoin, phenobarbitone and ascorbic acid on the elimination of misonidazole in man. *Clin. Pharmac. Ther.*, (in press).
- WORKMAN, P. (1979). Effects of pretreatment with phenobarbitone and phenytoin on the pharmacokinetics and toxicity of misonidazole in mice. *Br. J. Cancer*, **40**, 335-353.
- WORKMAN, P., BLEEHEN, N.M. & WILTSHIRE, C.R. (1980). Phenytoin shortens the half-life of the hypoxic cell radiosensitizer misonidazole in man: implications for possible reduced toxicity. *Br. J. Cancer*, **41**, 302-304.