since transurethral resection two weeks before. Is this appreciable reduction in morbidity?

Certainly he did not have to stay long in hospital, but who is to say that the current operative technique is more agreeable than open prostatectomy—it is done by the same surgeons, registrars, and house officers with intact prostates, who assert that retrograde ejaculation elicits the same sensation as normal. And did one of them consider asking me whether I wanted another child before they rendered my husband infertile? No—my consent was never sought. He was on the young side for prostatectomy and I am younger still. Moreover, he suffered no manifest chronic problem but was triggered into acute urinary retention by one over the eight . . . over the six . . . over the four on a few occasions in the past couple of years. The laser happy medical profession were of one accord in showing preferred intent for restoring his alcohol capacity.

It has been a gory fortnight—tissue, blood, and urine spilled down the outside of the catheter when he opened his bowels; a week postoperatively the renewed passing of blood clots threatened to stopper the works; and now, just as his most precious organ is recovering from the assaults up its tender shaft, he is having to carry his even more tender testicles in a suspension bandage while dieting on antibiotics, constipating pain killers, and laxatives.

Agreeable? He isn't!

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1 Chisholm GD. Benign prostate hyperplasia: the best treatment. *Br Med J* 1989;299:215-6. (22 July.)

Drug Points

Cardiac arrest associated with ranitidine

Dr ANGELA M HART (Department of Surgery, University College Hospital, London WC1) writes: Of the H₂ receptor blockers, ranitidine is the more potent antagonist and appears to lack some of the side effects seen with cimetidine. I describe a case in which normal use produced a potentially fatal reaction.

A 47 year old Bangladeshi man was admitted to the casualty department with sudden onset of epigastric pain. He had a one week history of similar, less severe pain alleviated by food. Otherwise he was fit, smoking 2 cigarettes/day, drinking minimal alcohol, and taking only salbutamol tablets (2 three times daily) for mild asthma diagnosed 10 years before. In particular he had no history of cardiac or electrolyte abnormalities. An emergency laparotomy was performed and a perforated duodenal ulcer diagnosed and treated. He was given 50 mg intravenous ranitidine three times daily. Postoperative recovery was uneventful until he suffered a cardiac arrest during administration of the fifth dose. Cardiopulmonary resuscitation was successful but he suffered one grand mal seizure immediately, secondary to hypoxia. After the arrest electrolyte and blood glucose concentrations and an electrocardiogram were all normal. An electrocardiogram five days after the arrest was also normal, and he was discharged after 10 days.

This case of cardiac arrest associated with ranitidine occurred in a patient who was relatively fit and apparently without any predisposing conditions. The ranitidine was diluted to 20 ml and given by slow injection each time. A worldwide review of those cases thought to be almost certainly related to the administration of ranitidine showed that one was associated with an anaphylactic reaction, one patient had an underlying pulmonary infarct, and two patients had predisposing cardiac problems. I have received no further reports from the Committee on Safety of Medicines. Cardiac

arrest has been reported with cimetidine, as have life threatening arrhythmias.¹ Minor side effects of ranitidine—headaches, nausea, and constipation (which usually resolve with continued therapy)²—are well documented, as are cases of ranitidine induced bradycardia,³ chorea,⁴ acute confusional episodes,⁵ and more recently chest pain.⁶ Now, all ranitidine data sheets are being updated to include a statement covering asystole in the side effects section.

The adverse cardiac effects of ranitidine may be due to H₂ receptor antagonism in coronary smooth muscle, via vasoconstriction⁷ or a rise in plasma histamine levels.⁸ Other mechanisms to be considered include a cholinergic action mediated by cholinesterase inhibition.⁹

I thank the department of international drug surveillance at Glaxo Group Research Limited for help.

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- 5 Davies WA. Mental confusion associated with ranitidine. *Med J Aust* 1983;iii:478.
- 6 Shrimp LA, Smith MA, Wahr DW. Ranitidine-induced chest pain. *Annals of Pharmacotherapy* 1989;23:224-6.
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- 8 Parkin JV, Ackroyd E-B, Glickman S, et al. Release of histamine by H₂ receptor antagonists. *Lancet* 1982;ii:938-9.
- 9 Hansen WD, Bertl S. Inhibition of cholinesterases by ranitidine. *Lancet* 1983;ii:235.

Hepatic injury caused by mianserin

Drs K OTANI, S KANEKO, H TASAKI, and Y FUKUSHIMA (Department of Neuropsychiatry, Hirosaki University Hospital, Hirosaki 036, Japan) write: There have been only three reported cases of hepatic injury associated with mianserin.¹⁻³ We have recently observed three more cases.

The first patient was a 46 year old man with depression. On the 14th day of receiving 30 mg of mianserin he developed a fever of 39.1°C. Diclofenac (100 mg/day) was prescribed for three days but had no effect. A blood analysis was then performed and cholestatic jaundice was found (table). Mianserin was discontinued and after six weeks the liver function was completely normal. The second patient was a 48 year old woman who took 20 mg of mianserin for three weeks to treat her depression. From the 22nd day the dose was increased to 30 mg and her depression was cured. Blood analysis on the 28th day showed an asymptomatic hepatic injury (table). Mianserin was discontinued, but it took three weeks before the liver function returned to normal. The third patient was a 63 year old woman. Her treatment started with 2 mg of flunitrazepam and 30 mg of mianserin, with the latter increased to 50 mg from

Results of liver function tests and plasma concentrations of mianserin and desmethylmianserin in present cases

Variable (and normal range)	Case 1	Case 2	Case 3
Aspartate aminotransferase (U/l) (<40)	115	74	121
Alanine aminotransferase (U/l) (<45)	352	541	385
Alkaline phosphatase (U/l) (30-110)	233	184	90
γ-Glutamyltransferase (U/l) (<60)	280	231	70
Total bilirubin (μmol/l) (3.4-24.0)	25.7	6.8	15.4
Direct bilirubin (μmol/l) (0-6.8)	12.0	1.7	3.4
Mianserin (nmol/l)	252	74	143
Desmethylmianserin (nmol/l)	39	43	42

the fifth day of treatment. On the 12th day of treatment blood analysis showed a hepatic injury (table). Mianserin was reduced to 30 mg, and 4 mg of bromazepam was then introduced. From the 19th day mianserin was further reduced to 20 mg. The liver function had returned to normal by the 26th day. Her depressive symptoms disappeared on the 33rd day and mianserin was discontinued.

All patients had normal liver function before mianserin treatment, and their hepatic injuries disappeared when mianserin was discontinued or the dose reduced. Investigations excluded other diseases such as viral hepatitis. It is therefore reasonable to consider that mianserin caused the hepatic injuries. With some drugs, such as valproate, toxic metabolites have been incriminated as the cause of hepatic injury,⁴ and monitoring concentrations of these metabolites may be useful to prevent hepatic injury. In fact, on the basis of an in vitro study Riley *et al* suggested that desmethylmianserin, the major metabolite of mianserin, is cytotoxic.⁵ Plasma concentrations of mianserin and desmethylmianserin in our patients were, however, similar to those in 20 other patients with no liver dysfunction, whose mean plasma concentration of mianserin was 105 nmol/l (range 41-213) and of desmethylmianserin 55 nmol/l (10-219).⁶ These findings suggest that the occurrence of hepatic injury does not depend on plasma concentrations of mianserin or desmethylmianserin, although in certain cases (such as case 3) the liver function may improve on reducing the dose. Therefore monitoring these compounds' concentrations does not seem to be useful. The manufacturer (Organon) knew of 138 cases of liver or biliary system disorders associated with mianserin treatment. Of these cases, only 23 showed an aspartate aminotransferase or alanine aminotransferase value ≥120 U/l. Considering the wide use of mianserin, the incidence of related hepatic injury is low, but our cases suggest that liver function be checked at an early stage of mianserin treatment.

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- 3 Urbain D, Rodzynek JJ, Wettendorf P, Meyer Ph, Delcourt A. Toxicité hépatique de la miansérine. *Rev Med Brux* 1984;6:39-40.
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Corrections

Hypercalcaemia in malignancy

The names of Dr S J Gallacher, Dr U Patel, and Dr I T Boyle were omitted from the letter by Dr Stuart H Ralston (15 July, p 181).

Enteropathy induced by non-steroidal anti-inflammatory drugs

An author's error occurred in this letter by Drs I Bjarnason and J M Gumpel (29 July, p 326). The second sentence in the third paragraph should have read "Differentiation from Crohn's disease is easy by scanning using leucocytes labelled with indium-111 as patients with Crohn's disease have an abnormal scan within four hours whereas the other patients show abnormal results 18 hours after the ¹¹¹In labelled leucocytes have been given."