LETTERS TO THE EDITOR

Anomalous short plasma elimination half life in a patient intoxicated with bismuth subcitrate

SIR,—The report by Playford *et al*¹ provides important information. There is only one other report of bismuth intoxication with the use of the subcitrate formulation in humans.² This report was marred by the absence of assay data.

The levels reported by Playford *et al* are well outside the values reported from other studies involving bismuth subcitrate (Table).³⁻⁸ These increased levels are consistent with a doubling of dose and renal impairment, if it is assumed that bismuth clearance reduces proportionally to creatinine clearance. Specifically, if upper steady-state limits of 58 µg/l are assumed in patients with normal renal clearance (≈120 ml/min) (see Table),⁶ and a creatinine clearance of 15 ml/min in the patient is assumed (case report value), then upper limits of 480 µg/l could be predicted. If daily doses were doubled, then values of 960 µg/l would be predicted, in close accord with the case report values of 880 µg/l.¹

There is, however, an anomaly related to estimated half life of elimination in plasma in this patient. We derive a value of 13–15 days from the published figure using terminal phase data. Previous reports of elimination half life values in both urine and plasma in the normal range of plasma bismuth concentrations⁶ and in intoxicated patients⁹ give values of 18–20 days. If renal elimination alone determines elimination half life, then a longer half life should have resulted with prolongation proportional to renal clearance change.

There is evidence in both animals and humans for excretion of bismuth into gut via bile on acute dosing.^{11,12} Such a mechanism of parallel, extrarenal elimination would need to be invoked to allow preservation of a short half life as reported. The apparent anomaly of a high level and a short half life can be resolved if altered absorption is proposed together with parallel hepatic and renal clearance. The altered absorption in this patient reported by Playford and coworkers¹ may be explained by upper gastrointestinal surgery with rapid gastric emptying.

Because of direct relevance to this discussion we present preliminary data from three

patients given 430 mg daily of bismuth subcitrate (Denol) for four days after cholecystectomy and placement of a T-tube in the common bile duct. Blood, urinary, and biliary collections were made over six hours after the morning dose on the fifth day. Relative clearances in urine and bile after assay of samples¹³ are shown in the Figure.

Biliary (B) and urinary (U) clearances (ml/min) of bismuth in each of three patients (1, 2, and 3). These patients had a biliary T-tube in the common bile duct after cholecystectomy and were given 107.7 mg bismuth in the form of chew colloidal bismuth subcitrate tablets (Denol) four times a day for four days.

Until another class of agents is discovered with equal efficacy¹⁴⁻¹⁷ there will be a need to continue the use of bismuth in type B gastritis and ulcer disease.¹⁸ There is a need to understand the processes of bismuth handling before restriction policies can be made. Caution must be exercised in patients with renal impairment and possibly hepatic impairment. The ready availability of simple assays¹³ allows plasma monitoring to be used to optimise safe usage, according to accepted plasma level guidelines.¹⁹

A J MCLEAN
S ISLAM
Clinical Pharmacology Department,
Alfred Hospital,
Prahan, Victoria, 3181
Australia

J R LAMBERT
Monash University
Department of Medicine

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Macrophage activity in inflammatory bowel disease

SIR,—We reply to the letter from Dr Andrew Williams (*Gut* 1990; 31: 481) in which he disagrees with the conclusion in our paper¹ that the majority of macrophages isolated from normal colon and ileum are downregulated. This statement is based on the results presented in the paper and evidence from other studies as quoted in the discussion.

Our study shows that a significantly greater proportion of macrophages isolated from mucosa with active ulcerative colitis and Crohn's disease (and not just Crohn's disease) were able to undergo respiratory burst compared to those isolated from normal mucosa. In the latter, a large proportion did not show evidence of a release of oxygen radicals in response to three different triggers. Despite stimulation with interferon-gamma (perhaps the most potent activator of macrophages), a large proportion of macrophages from normal

Plasma concentration after chronic treatment with colloidal bismuth subcitrate

Reference	No of subjects	Duration of treatment (weeks)	Formulation	Range of steady-state concentration (µg/l)
Lee (1981)	24	4–6	Liquid	3–35
Hamilton <i>et al</i> (1983)	20	6	Chew tablet (4×1)	5–51
Dekker <i>et al</i> (1986)	76	4	Chew tablet (4×1)	3–34*
	67	4	Swallow (coated) (4×1)	2–21*
Froomes <i>et al</i> (1989)	12	6–8	Chew tablet (4×1)	8–58
Gavey <i>et al</i> (1989)	9	6	Swallow (coated) (2×2)	4–38
Nwokolo <i>et al</i> (1989)	6	4–18	Swallow (coated) (2×2)	2–12

* Represents peak blood concentration rather than steady-state concentration.