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Nephrotoxicity and Hepatotoxicity of Histamine H_2 Receptor Antagonists

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Contents

Abstract

The extensive use of selective histamine H_2 receptor antagonists provides a unique opportunity to describe very rare adverse drug reactions.

Although mild elevation of serum creatinine level following the administration of cimetidine is relatively common, acute interstitial nephritis (AIN) is a rare hypersensitivity reaction. There have been 25 published reports of AIN associated with H_2 antagonist therapy and we also identified 16 cases from the Australian Adverse Drug Reaction Advisory Committee (ADRAC) database. AIN was reported most commonly following cimetidine administration. AIN was supported by renal biopsy in 28 patients and by rechallenge in 6. H_2 antagonist–induced AIN was more commonly reported in men older than 50 years. In the majority of cases the onset was within 2 weeks of initiation of therapy (1 day to 11 months). The clinical manifestations were nonspecific including sterile pyuria, elevated

erythrocyte sedimentation rate, fatigue, proteinuria and leucocytosis whereas rash, arthralgia and flank pain were rarely reported.

There were 170 cases of hepatotoxicity following H_2 antagonist administration reported to ADRAC. These were more common following ranitidine and included cholestatic, hepatocellular and mixed reactions. Hepatotoxicity was proven following liver biopsy in several cases published in the literature and in 15 cases reported to ADRAC. Hepatotoxicity recurred upon rechallenge in 6 cases.

Generally, renal and hepatic adverse effects resolved quickly after cessation of H_2 antagonist therapy and did not require specific treatment. Nephrotoxicity and hepatotoxicity following administration of an H_2 antagonist is rare and a high index of suspicion is necessary for early detection. Now that many H_2 antagonists are available over the counter, awareness of these conditions and early detection with cessation of H_2 antagonist therapy would appear paramount.

1. History

The presence of 2 histamine receptors was postulated by Folkow in 1948 on the basis that conventional antihistamines do not block all histamine-induced actions, including gastric acid secretion.[1] The subsequent development of histamine H_2 receptor antagonists by Black and colleagues in 1972[2] followed extensive testing of many compounds.[3] These agents that can inhibit gastric acid secretion have revolutionised gastrointestinal therapeutics.

H_2 receptors have now been identified in many tissues including the gastric mucosa, ileum, uterus, bronchial musculature, heart, kidney, brain, liver, endothelial cells, adipocytes, T suppressor cells and parathyroid cells.[4] The role of H_2 receptors in the stomach has been extensively studied. Histamine is released from enterochromaffin-like (ECL) cells and is the principal paracrine stimulant of gastric acid secretion. Histamine directly activates H_2 receptors located on the basolateral membrane of the acid-secreting parietal cells.[5,6] Activation of the G-protein coupled H_2 receptor promotes mainly the adenylate cyclase pathway with activation of the hydrogen-potassium ATPase proton pump.[7]

Specific drugs acting as antagonists of histamine at H_2 receptors were developed through application of rational drug design. Imidazolyalkyguanidines, isothioureas and carboxamides were found to be partial agonists of the H_2 receptor. Lengthening the side chain and replacing the strongly basic group with nonbasic moieties lead to molecules with antagonistic activity including cimetidine and later ranitidine, famotidine and nizatidine (fig. 1).

Early clinical trials in the early and mid 1970s confirmed the effect of cimetidine on suppression of gastric acid secretion, whether basal, nocturnal, induced by food or other stimuli.[4,8,9] By the late 1970s the effects of cimetidine on ulcer healing had been confirmed in phase III clinical trials.[10]

For over 3 decades, H_2 antagonists have been prescribed for peptic ulceration, gastro-oesophageal reflux and dyspepsia. They are amongst the most widely prescribed medications in the history of modern medicine and cimetidine became the largest selling drug in the world.[4] In Australia, ranitidine was the most commonly prescribed drug after paracetamol (acetaminophen) and paracetamol/codeine in 1997 to 1998 according to statistics from the Australian Pharmaceutical Benefits Scheme. Despite the emergence of proton pump inhibitors and antibacterial therapy for *Helicobacter pylori*, the use of H_2 antagonists has continued to increase. In the period from 1990 to 1999, the defined daily doses/1000 population/day for H_2 antagonists increased from about 7 to 26 in Australia (fig. 2).

The extensive use of H_2 antagonists provides a unique opportunity to describe very rare adverse drug reactions in considerable detail. In general, these drugs are relatively safe although there are reports concerning adverse effects on the CNS, gastrointestinal tract, haematopoietic system and the

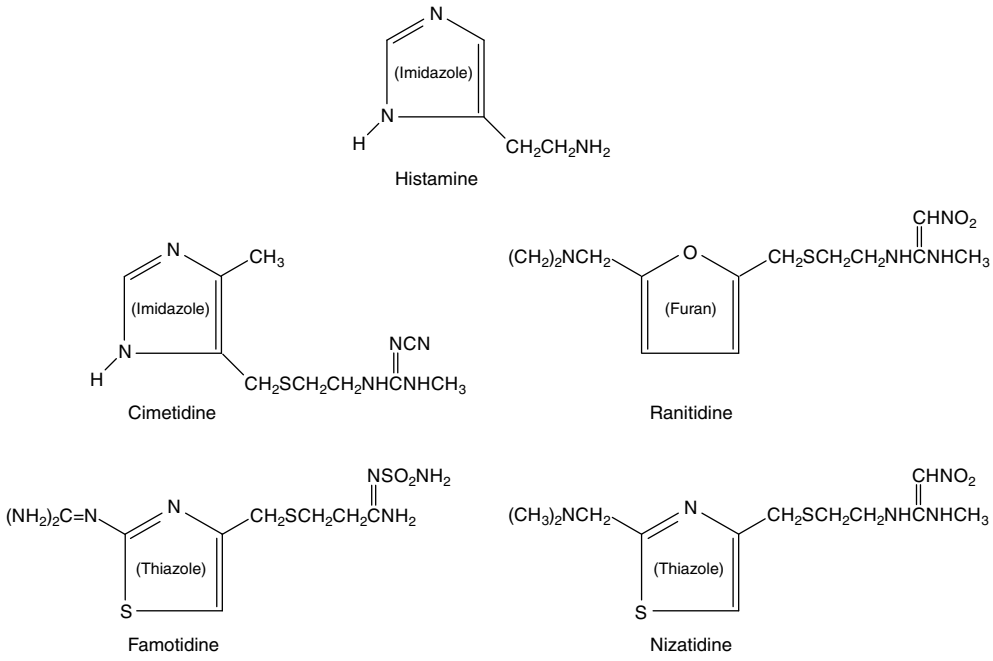

Fig. 1. The chemical structures of histamine, cimetidine, ranitidine, famotidine and nizatidine.

heart.[11,12] The adverse effects are not usually serious and resolve with cessation of medications. It has been estimated that between 2 to 3% of people who take H_2 antagonists experience adverse effects[13-15] and the incidence of adverse events in clinical trials was similar to placebo.[11,15,16] In general, H_2 antagonists are associated with a surprisingly low rate of adverse reactions in relation to their frequency of use and the wide distribution of H_2 receptors in many tissues.

Mild transient and reversible increases in serum creatinine levels have been observed in about 60% of patients taking cimetidine during the first weeks of treatment but acute renal failure is rare.[12,17-19] In late 1970s, after cimetidine was first released, the incidence of acute interstitial nephritis (AIN) was estimated to be fewer than 0.1 cases per 100 000 patients on the basis of worldwide spontaneous reporting system.[20] Drug-induced AIN accounts for 3.6 to 8% of all cases of acute renal failure[21,22] and AIN was found in 25% of renal biopsies in patients with drug-induced acute renal failure.[23] Hepatotoxicity associated with H_2 antagonists also is very rare. There have been reports of increases in serum transaminase activities,[18] idiosyncratic hepatotoxicity and, of course, drug interactions related to inhibition of the hepatic cytochrome P450 enzymes.[24,25]

In this paper, we review the association of H_2 antagonists with the rare adverse effects of hepatitis and nephritis. The data for this analysis were obtained from a MEDLINE database search (1970 to 1999) followed by a manual search of bibliographies of pertinent articles. We also searched the Australian Adverse Drug Reaction Advisory Committee (ADRAC) database from 1972 to 1999.

2. Nephrotoxicity

2.1 Cimetidine and Elevated Creatinine Level

Cimetidine therapy in healthy volunteers and patients with duodenal ulcer disease is associated with mild (rarely greater than 177 μmol/L) and often transient elevation of serum creatinine level.[10,12,18,19,26]

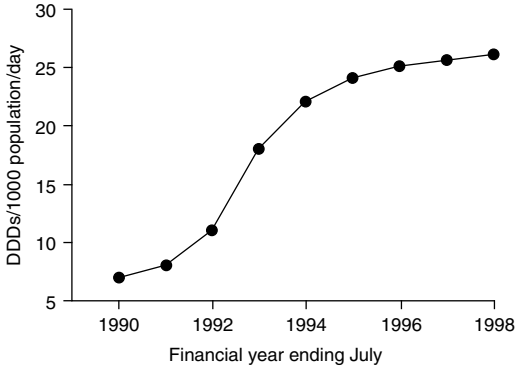

Fig. 2. Defined daily doses (DDD)/1000 population/day for histamine H_2 receptor antagonists. The statistics were obtained from the Pharmaceutical Benefits Scheme of Australia.

This is not usually accompanied by other abnormalities of renal function such as blood urea nitrogen, glomerular filtration rate, inulin clearance and chromium-51 ethylenediamine tetra-acetic acid (^{51}Cr-EDTA) clearance.[19,27,28] Elevation of serum creatinine level has been observed in as many as 59% of patients receiving cimetidine but is also common in placebo recipients.[12] Often the creatinine level returns to normal with continued exposure to cimetidine and therapy had to be discontinued because of elevated creatinine levels in only 4 case reports.[29,30]

The increase in creatinine level is not explained by interference of cimetidine in techniques used to measure creatinine level or by increased endogenous synthesis of creatinine.[18] Instead, it is believed that cimetidine interferes with the tubular secretion of creatinine.[18,19,31]] Evidence for this mechanism includes: (i) cimetidine is secreted in the distal renal tubule in vitro;[31,32] (ii) the effect is dose-related;[10,19,26] and (iii) in healthy volunteers after cimetidine administration creatinine clearance decreased but inulin and ^{51}Cr-EDTA clearance was unchanged[31] and the creatinine clearance/inulin clearance ratio decreased.[28] However, in individuals with normal glomerular filtration rate only a fraction of the rise in serum creatinine level can be attributed to inhibition of tubular secretion because only a small fraction of excreted creatinine is eliminated via distal tubular secretion.

Ranitidine and cimetidine are both weakly basic organic molecules and are excreted mainly by distal tubular secretion.[33] However, ranitidine does not cause significant elevations of serum creatinine level.[14,34] Moreover, in renal transplant patients the creatinine to inulin ratio did not alter after 1 week of ranitidine whereas following 1 week of cimetidine it decreased from 1.8 to 1.4.[35] It has been suggested that ranitidine does not cause changes in creatinine level because it is used in smaller doses that do not affect tubular secretion.[36] A similar mechanism of competition for renal tubular secretion may explain the observation that cimetidine and ranitidine but not famotidine decrease the clearance of procainamide by 44 and 18%, respectively.[37,38]

There are histamine receptors in the kidney and infusion of histamine increases renal blood flow, an effect that can be abolished by inhibitors of prostaglandin synthesis.[39,40] These findings suggest that prostaglandins may serve as mediators of renal histamine-induced effects, therefore prostaglandins and renal perfusion may mediate the effects of cimetidine on renal function.[41]

In clinical practice, elevation of creatinine level is not usually considered to be significant and does not warrant discontinuation of therapy.[11,12]

2.2 Acute Interstitial Nephritis

2.2.1 Literature Reports

We found 25 published reports of AIN associated with H_2 antagonists: 20 cases with cimetidine, 4 with ranitidine, and 1 with famotidine (table I). There were 14 men and 10 women (in one case gender was not presented), aged between 17 and 80 years (mean age 58.3 years). They developed AIN between 2 days and 11 months after commencing H_2 antagonist therapy.

The diagnosis of AIN was confirmed by renal biopsy in 18 cases. In the other cases the diagnosis was suspected on clinical grounds and supported by rapid improvement of patients' condition following drug withdrawal and/or rechallenge (5 cases).

Table I. Characteristics and laboratory findings in 25 patients reported in the literature with acute interstitial nephritis associated with histamine H_2 receptor antagonist therapy

Reference	Year	Age	Gender	Underlying condition	Daily dose (mg)	Length of therapy	Peak level		Recovery level		Biopsy	Comments
							urea (mmol/L)	creatinine (μmol/L)	urea (mmol/L)	creatinine (μmol/L)		
Cimetidine												
McGowan & Vermillion[42]	1980	21	M	DU	1200	2 wk	13.2	248		185.6	+	
Linton et al.[22]	1980	NS	NS		NS	NS	NS	495		88.0	+	
Hake[43]	1981	57	M	Peptic oesophagitis	NS	1 mo	NS	416		114.9		
Richman et al.[44]	1981	67	M	Dyspepsia, secondary corticosteroid therapy	900	3 wk	28.9	698	7.5	14.4		Rechallenge
Rudnick et al.[45]	1982	59	M	Peptic ulcer	1200	3 wk	8.2	592	6.4	300.6		Rechallenge
	1982	74	M	Erosive oesophagitis	1200	1 mo	31.4	716	8.9	177.2	+	
Payne et al.[46]	1982	67	M	DU, bleeding	1000	2 mo	19.0	550	7.6	150	+	Rechallenge: ALP 700 U/L
				Abdominal pain	1000	3 d	10.2	260	5.6	180		ALP 1165 U/L
Ali et al.[47]	1982	73	F	Reflux oesophagitis, Stricture	600	2 wk	22.5	406			+	
Pitone et al.[48]	1982	68	F	Reflux oesophagitis	900	3 wk	NS	495			+	Rechallenge
Potter & Westby[49]	1983	67	M	Peptic oesophagitis	1200	2 wk	NS	451		141.4		ALP 540 U/L ESR 140 mm/h
Kaye et al.[50]	1983	80	F	Ulcerative oesophagitis	1200	2 wk	19.3	362		159	+	
Watson et al.[51]	1983	42	M	DU	900	11 mo	70.7	1733		114.9	+	Polymyositis
Morley & Ballou[41]	1983	17	F	Lupus nephritis	1200	4 d	10.0	239	≈ 7.5	≈ 100		
Handa[21]	1986	43	M	Peptic ulcer	NS	42 d	16.4	380		150.3	+	
	1986	61	F	Hypertension	800	80 d	36.4	1176		79.6	+	
	1986	66	M	Peptic ulcer Pneumonia	NS	30 d	42.8	769		150.3	+	
Ozawa et al.[52]	1987	48	M	Reflux oesophagitis, hiatus hernia	1200	26 d	14.3	504			+	Rechallenge ALP 329 U/L ESR 130 mm/h
Mullen[53]	1992	52	M	DU	NS	10 wk	11.8	290	NS	NS		ESR 80 mm/h
Koarada et al.[54]	1992	52	F	GU	600	1 mo	18.1	672			+	

Continued next page

Table I cont.

One patient also had underlying lupus nephritis.[41] The daily dose of cimetidine varied between 800mg and 1200mg and the daily doses of ranitidine and famotidine were 300mg and 40mg respectively.

The peak level of urea ranged between 8.2 and 70.7 mmol/L (mean 24.8 mmol/L). Considered separately, the mean peak urea concentration was 26.9 mmol/L for cimetidine and 16.7 mmol/L for ranitidine. The peak level of creatinine ranged between 106.1 and 1732 μmol/L (mean 577.2 μmol/L). The mean peak creatinine was 613 μmol/L for cimetidine and 336 μmol/L for ranitidine.

2.2.2 Australian Reports

A search of the ADRAC database revealed that between 1 November 1972 and 1 October 1999 there were 716 reports of adverse reactions associated with cimetidine (1976 to 1999), 1476 reports with ranitidine (1980 to 1999) and 338 reports with famotidine (1989 to 1999).

There were 11 reports of AIN associated with cimetidine, 4 with ranitidine and 1 with famotidine. During the period from 1972 to 1999 there were a total of 145 reports of drug-induced AIN, therefore, 11% of all reported drug-induced cases of AIN were associated with the use of H_2 antagonists. This figure is comparable with those reported in the literature. Cimetidine was associated with 1 of 9 cases of drug-induced AIN (11%) in 1 study[22] and in 3 of 10 patients (30%) in another.[21]

Table II summarises the main clinical characteristics of the ADRAC reports. There were 8 men and 8 women, aged from 31 to 86 years (mean 59.2 years). The length of therapy before the onset of renal impairment varied from 1 day to 9 months. The daily dose of cimetidine varied from 400mg to 1000mg, ranitidine from 150mg to 300mg, and for famotidine it was 40mg.

None of the patients had a pre-existing renal disease but all had unexplained and sudden deterioration in renal function with rapid recovery on withdrawal of the H_2 antagonist. Nine patients were taking no other medication that could have caused acute renal impairment. The diagnosis of AIN was confirmed by renal biopsy in 10 cases (although in

Table I. Contd.

Reference	Year	Age	Gender	Underlying condition	Daily dose (mg)	Length of therapy	Peak level		Recovery level		Biopsy	Comments
							urea (mmol/L)	creatinine (μmol/L)	urea (mmol/L)	creatinine (μmol/L)		
Kitahara et al.[55]	1999	63	M	GU	800	3 wk	NS	177			+	
Ranitidine												
Freeman[56]	1988	72	M	Duodenal erosions, celiac sprue	300	3 mo	25.3	195	13.2	141	+	Prednisolone
Gaughan et al.[57]	1993	71	M	Abdominal pain Cholecystitis	300	5 d	22.5	301			+	Prednisolone
Neelakantappa et al.[36]	1993	39	F		300	3.5 wk	16.1	601			+	Prednisolone
Karras[58]	1994	67	F	Epigastric pain	300	2 d	11.4	106	NS	NS		ALP 112 U/L
Famotidine												
Hirayama et al.[59]	1998	72	M	Gastric cancer, GU	40	10 d		707		123.8	+	

ALP = alkaline phosphatase; **DU** = duodenal ulcer; **ESR** = erythrocyte sedimentation rate; **F** = female; **GU** = gastric ulcer; **M** = male; **NS** = not stated; **+** = biopsy performed.

Table II. Characteristics and laboratory findings in 16 patients with acute interstitial nephritis associated with histamine H_2 receptor antagonists reported to Australian Adverse Drug Reaction Advisory Committee

Patient age	Year reported	Gender	Underlying condition	Dose daily (mg)	Length of therapy	Peak level		Recovery level		Biopsy	Comments
						urea (mmol/L)	creatinine (μmol/L)	urea (mmol/L)	creatinine (μmol/L)		
Cimetidine											
66	1978	F	DU	800	2 mo	15.2	220		150		ALP 228 U/L
NS	1982	F	DU	1000	3 mo					+	
60	1982	M	GI bleeding	600	2 d					+	Maculopapular rash
54	1983	M	PUD	400	9 mo		390			+	
50	1983	M		400	3 mo	23.2	541				
57	1983	M		400	4 mo					+	
74	1984	M	GU	800	NS	15.4	290			+	
68	1986	F	PUD	800	NS		300		N		ESR 105 mm/h; rechallange; corticosteroids
67	1994	F		400	NS		1390		170		
63	1996	F	Dyspepsia	400	NS	14.7	310	4.7	113	+	ESR 140 mm/h
40	1999	M	Dyspepsia	1200	5 d	26.7	775	7.1	140	+	ESR 111 mm/h, CRP 255 mg/L, bilirubin 60 mmol/L, ALP 161 U/L, ALT 72 U/L
Ranitidine											
66	1991	F		300	5 d		910		280		
31	1993	M		150	6 d	8.5	200		110		
86	1995	F		300	2 d	9.2	382			+	
47	1996	F		300	4 d	24.7	396	15.4	142	+	ALT 738 U/L; GGT 169 U/L
Famotidine											
NS	1997	M	Dyspepsia	40	14 d		500		120	+	

ALP = alkaline phosphatase; **ALT** = alanine transferase; **CRP** = C-reactive protein; **DU** = duodenal ulcer; **ESR** = erythrocyte sedimentation rate; **F** = female; **GGT** = γ-glutamyl transferase; **GI** = gastrointestinal; **GU** gastric ulcer; **M** = male; **NS** = not stated; **PUD** = peptic ulcer disease; **+** = biopsy performed.

2 cases the results were not submitted) and by rechallenge in 1 case.

All patients had moderate to severe renal failure with elevated levels of blood urea (mean 17.2 mmol/L; range 8.5 to 26.7 mmol/L) and serum creatinine (mean 508 μmol/L; range 200 to 1390 μmol/L).

2.2.3 Clinical Features

Because of the small numbers of cases we combined the 25 literature reports with the 16 ADRAC reports (table III). The diagnosis of AIN was supported by renal biopsy in 28 cases and by rechallenge in 6 cases.

The mean age in the combined series was 58.6 years (range 17 to 86 years), and only 19% were aged 50 years or younger. 39% were women (F : M = 2 : 3). Therefore, this adverse effect appears to be reported more frequently in older men although the prevalence cannot be assessed in the absence of drug utilisation data. The onset of clinical manifestations after exposure to the drug was variable. It ranged from 1 day to 11 months. However, in about 55% of cases the onset was less than 2 weeks.

There does not appear to be a relationship between the dose of H_2 antagonist and the degree of renal failure (fig. 3). The mean peak level of blood urea with cimetidine was 23.2 mmol/L, and ranitidine was 16.8 mmol/L. The mean peak level of creatinine with cimetidine was 546 μmol/L; with ranitidine 386 μmol/L; and with famotidine 604 μmol/L. Overall, it does not appear that there is any difference in the severity of renal disease caused by these 3 agents although the number of cases is too small for a definitive conclusion.

The presenting clinical features were nonspecific. They included fever (85%), fatigue and generalised malaise (67%), myalgia (21%), nausea (19%), loss of appetite (22%) and night sweats (19%). Other symptoms commonly associated with drug-induced AIN such as rash, arthralgias and flank pain were rarely reported. There are case reports of H_2 antagonist–induced AIN associated with low back pain and a pruritic maculopapular rash,[58] costovertebral tenderness,[53] and bilateral episcleritis.[49] The classic triad of fever, skin rash and arthralgias that has been described in about one-third of patients with methicillin-induced AIN has never been reported in AIN associated with H_2 antagonists.

Urinary output was variable, with acute-onset oliguria reported in 14% of cases and polyuria in 7%. This is less than in other cases of drug-induced AIN where the prevalence of oliguria is 40 to 80%.[22,60,61] An unusual case of ranitidine-induced AIN with prominent proximal tubular dysfunction has been reported where the patient had renal tubular acidosis, renal glucosuria, amino aciduria, phosphaturia and uricosuria.[36]

The most common findings in urinalysis were sterile pyuria (100%) and mild to moderate proteinuria (80%). The highest reported level of protein excretion was 1400mg per 24 hours.[45] Proteinuria in the nephrotic range, which is common in AIN induced by nonsteroidal anti-inflammatory drugs (NSAIDs) or ampicillin, has not been reported in AIN secondary to H_2 antagonists.

In addition, microhaematuria (50%) and eosinophiluria (55%) were occasionally noted. Eosinophiluria is often considered to be an important sign of drug-induced AIN however, we noted that only about half of the cases were associated with eosinophiluria. Eosinophiluria may not be a useful test because its detection depends on the technique used (for example, Hansel's stain is 5 times more sensitive than Wright's stain[62]) and it is found in other diseases associated with AIN such as chronic interstitial nephritis, eosinophilic cystitis, transplant rejection.[63] Mild to moderate leucocytosis (11.6 to 16.2/μl) was reported in 63% of cases and eosinophilia was reported in 56% of cases. An elevated erythrocyte sedimentation rate (ESR) [80 to 145 mm/h] was a consistent finding in almost all reports.

In general, these clinical characteristics lack specificity. It has been suggested that a distinguishing feature of H_2 antagonist–induced AIN is low urinary sodium level and elevated urine-to-plasma osmolality ratio. This has been disputed.[22] Rechallenge and renal biopsy remain the gold standard criteria for diagnosis.

Table III. Clinical and laboratory features in 41 patients with histamine H_2 receptor antagonist–induced acute interstitial nephritis from the database of the Australian Adverse Drug Reactions Advisory Committee and literature reports

Clinical features	(% of patients)	Laboratory features	(% of patients)
Age in years (range)	58.6 (17-86)	**Urinalysis**	
Male : female ratio	3 : 2	Proteinuria	80
Pre-existing renal disease	3	Haematuria	50
Onset within 2 weeks	55	Sterile pyuria	100
Daily dose:		Eosinophiluria	55
Cimetidine	400-1200mg	**Full blood count**	
Ranitidine	150-300mg	Leucocytosis	63
Famotidine	20-40mg	Eosinophilia	56
Fatigue, weakness	67	Elevated ESR	100
Fever	85	**Electrolyte and metabolic abnormalities**	
General myalgia	21	Hyponatraemia	5
Skin rash	3	Fanconi syndrome	3
Anorexia, nausea, vomiting	19	**Immunological studies**	
Back pain	5	Antinuclear antibodies	0
Dysuria	18	Anti-DNA	0
Acute-onset oliguria	14	Immunoglobulin E	0
Polyuria	7	C3, C4	0
Episcleritis	3	Anti-tubular basement membrane antibodies	0
Biopsy	64	Antineutrophil cytoplasmic antibodies	3
Rechallenge	15	**Abnormal liver function**	
Dialysis used	5	Increased ALP level	15
Corticosteroid therapy used	18	Increased ALT level	3
		Increased GGT level	5
		Increased bilirubin level	3

ALP = alkaline phosphatase; **ALT** = alanine transferase; **C** = complement; **ESR** = erythrocyte sedimentation rate; **GGT** = γ-glutamyl transferase.

2.2.4 Renal Biopsy

Renal biopsy samples examined by light microscopy reveal intense interstitial nephritis characterised by heavy interstitial infiltrate of plasma cells – often enlarged and active, lymphocytes, macrophages, eosinophils and polymorphonuclear leucocytes. The infiltrate is more severe around the tubules and inflammatory cells sometimes infiltrate the tubular basement membrane. Intraluminal leucocyte casts and eosinophilic material were seen. The glomeruli and vasculature were normal in all cases.

Immunofluorescence studies using antisera to immunoglobulins (Ig) G, A and M, complement C3, C4, and C1q, fibrinogen, albumin, properdin showed no staining of glomerular or tubular basement membranes. The absence of evidence of deposition of immunoglobulin, complement of fibrinogen suggests that none of the reported cases were secondary to antibody-mediated interstitial nephritis.

Electron microscopy of the glomeruli did not reveal any electron-dense deposits, swelling of fusion of epithelial foot processes or endothelial cell proliferation, except in 1 report associated with cholecystitis.[57] Mesangial proliferation and deposits in the mesangium or tubular basement membrane were not seen. However, in 1 case report of AIN induced by ranitidine, electron microscopy showed focal fusion of epithelial cell foot processes and this was associated with non-nephrotic proteinuria (1.3 g/day).[57] This has also been described in NSAID-induced AIN.[64,65] Diffuse epithelial cell foot process fusion and nephrotic syndrome have been reported in renal disease associated with ampicillin, interferon-α and NSAIDs.[21]

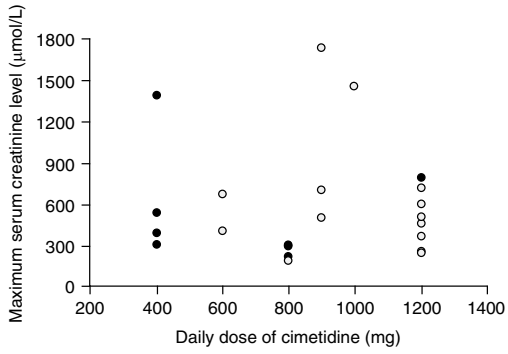

Fig. 3. The relationship between maximum serum creatinine level and the daily dose of cimetidine. The data shown in this figure are derived from the data presented in tables I, II and III [closed circles = data from the Australian Adverse Drug Reaction Advisory Committee; open circles = data from the literature]. There was no significant relationship between daily dose and serum creatinine level.

2.2.5 Rechallenge

In 5 literature cases[43,45,46,48,52] and in 1 case reported to ADRAC, re-exposure to cimetidine resulted in a prompt return of clinical features (fever, pyuria, proteinuria), elevation of urea and creatinine levels, and eosinophilia. According to Rudnick et al.,[45] there is an additional unpublished report of an elderly patient receiving cimetidine who developed fever, dysuria and mild renal failure. The symptoms improved following discontinuation of the drug and anuric renal failure developed after re-exposure. Renal biopsy revealed AIN. Rechallenge with the drug 6 months later caused fever, abnormal urinary sediment and elevation of creatinine level. There is 1 case of famotidine-induced AIN where re-exposure produced a substantial rise in serum creatinine level.[59]

Interestingly, challenge with ranitidine in at least 2 patients with AIN secondary to cimetidine did not produce clinical relapse.[47,49] This suggests that it may be possible to substitute H_2 antagonists if AIN occurs and continuation of drug therapy is essential.

2.2.6 Mechanisms

Drug-induced AIN is generally thought to be mediated by hypersensitivity although the mechanisms have not been fully elucidated and it may be more complex for H_2 antagonists. For example, human lymphocytes possess H_2 receptors. T cells that express H_2 receptors have been identified as CD8+ cells, and those with the highest level of H_2 receptors are CD25+ cells.[66] Histamine has many immunological effects.[67-69] Histamine activates suppressor T lymphocytes, suppresses cytotoxic T lymphocytes, promotes antibody-dependent cellular cytotoxicity of natural killer cells and may inhibit antibody production. The effects of histamine that appear to mediated through H_2 receptors include effects on lymphocyte proliferation, T cell-mediated cytotoxicity of allogeneic target cells and production of lymphokines and immunoglobulin.[70,71] In particular, histamine suppresses interleukin-12 secretion and stimulates interleukin-10 secretion via effects on the H_2 receptor. This might shift the T helper (T_H) 1/T_H2 ratio toward T_H2 dominance and stimulate T_H2-mediated allergic reactions.[72]

Subsequently, it was found that H_2 antagonists modulate the function of the immune system. Patients receiving cimetidine have enhanced cell-mediated immunity as evaluated by increased response to skin-test antigens, restoration of sensitivity after development of acquired tolerance, and increased responses of lymphocytes to nitrogen stimulation.[73] The proposed mechanisms of immunomodulative effects of H_2 antagonists include: (i) an inhibitory effect on suppressor T lymphocyte activity; (ii) an increase in interleukin-2 production;[74,75] (iii) enhancement of natural killer cell activity;[66] and (iv) an increase in immunoglobulin production.[70]

The order of potency of these immunomodulating effects is cimetidine > ranitidine > famotidine.[68] Cimetidine is capable of immunoregulating T cell-mediated proliferative responses in both humans and mice.[74] It has been shown that cimetidine has anti-proliferative effects in gastric cancer[69] and increases lymphocyte infiltration of primary colorectal carcinoma.[76] The immunomodulatory effects of H_2 antagonists have been reported in diseases such as AIDS, common variable hypogammaglobulinaemia, chronic mucocutaneous candidiasis, burns, herpes simplex, recalcitrant warts, pre-eclampsia and sclerosing panencephalitis.[77-79]

The normal renal interstitium contains 2 types of cells responsible for the initiation of an immune response to foreign antigens: (i) antigen–presenting cells; and (ii) T lymphocytes. Mechanisms involving humoral- or antibody-dependent hypersensitivity reactions in AIN have been reported.[80] However, it is generally believed that cell–mediated mechanisms are more important in most cases of drug-induced AIN. Cimetidine has been associated with immediate–type hypersensitivity[81] and IgE–mediated fever where the mechanism of hyperthermia was confirmed by re-challenge tests with cimetidine and ranitidine, markedly increased serum IgE level, positive skin tests and positive lymphocyte stimulation tests. However, this patient did not have AIN.[82] The absence of rash in most cases of H_2 antagonist–induced AIN would seem to exclude immediate-type (type I) hypersensitivity as a mechanism.

Furthermore, the usual absence of antibodies directed against tissue antigens, immune complex deposition or complement activation suggest that humoral mechanisms (type II and type III) are not involved. However there is 1 case of cimetidine–induced and biopsy proved AIN that was associated with antineutrophil cytoplasmic antibody (ANCA), reactive with myeloperoxidase, elastase, and lactoferrin. Cessation of cimetidine resulted in complete resolution of renal abnormalities and the titres of ANCA became almost undetectable.[55] The only other reports of AIN associated with ANCA followed administration of hydralazine,[83] omeprazole[84] and ciprofloxacin.[85]

On the other hand, cimetidine is a potent stimulator of delayed hypersensitivity.[86-89] In animal models of AIN that have been mediated by delayed hypersensitivity the histological findings are intense mononuclear cell infiltration and absence of immunoglobulin deposition.[90-92] This is similar to AIN induced by H_2 antagonists in humans.

In the majority of reported cases of AIN with renal biopsy specimens, the interstitial cellular infiltrate was been found to be predominantly T lymphocytes.[51,93-97] In some cases the T lymphocytes were categorised as cytotoxic/suppressor cells.[94,95] The intense infiltrate of plasmocytes into the interstitium could indicate indirect polyclonal activation of B cells.[55]

Cell-mediated immunity was well documented in 1 patient with cimetidine-induced nephropathy and polymyositis.[51] There was a marked increase in the proportion of cytotoxic/suppressor T lymphocytes in the inflammatory infiltrates in the kidney and muscle. An increased number of histocompatability DR-antigen positive T cells in the circulation was also noted, a feature of immune activation.[98] Small focal areas with IgE-producing plasma cells were identified in the inflammatory infiltrates in renal and muscle biopsy specimens. On the sixth day of steroid therapy the T cell subset ratios in the blood normalised and the proportion of DR–antigen positive T cells was below 1%. Interestingly, when lymphocytes were incubated with cimetidine, stimulation of lymphoblastogenesis, lymphokine production, and inhibition of leucocyte migration occurred. This has not been observed with lymphocytes from healthy people.

2.2.7 Treatment

Prompt recognition of AIN and cessation of H_2 antagonist therapy are the most important aspects of therapy. Rapid improvement follows discontinuation of H_2 antagonist therapy within days or weeks. Although renal damage may be severe, haemodialysis is rarely required – only 2 patients in this series required dialysis.[44,51] Corticosteroids were administered to 7 patients (17.5%), 4 with cimetidine-induced AIN and 3 with ranitidine-induced AIN. Early studies support the use of corticosteroids in drug-induced AIN,[61,99,100] however, this approach has not become widely accepted. As with most cases of drug-induced AIN, the prognosis in H_2 antagonist–induced AIN is very good, provided the drug is stopped. There were no reports of deaths in our series of cases.

3. Hepatotoxicity

3.1 Literature Reports

One H_2 antagonist in early clinical development, oxmetidine, was removed from clinical trials be-

cause of hepatotoxicity in 1 to 4% of patients and demonstrated dose- and time-dependent cytotoxicity in *in vitro* studies.[101,102] Recently, ebrotidine was withdrawn after 18 months because of hepatotoxicity with elevated aminotransferase and bilirubin levels associated with centrolobular necrosis (2 cases) or massive necrosis (1 case) on liver biopsy.[103] However, in general reports of hepatotoxicity associated with H_2 antagonist therapy are very rare.[24,38] It has been estimated that cimetidine-induced hepatotoxicity occurs once for every 300 000 to 600 000 prescriptions, ranitidine-induced hepatotoxicity occurs once for every 75 000 to 150 000 prescriptions[24] and ranitidine-associated acute hepatitis in 1 in 100 000 patients.[15] According to the manufacturers, the rate of hepatitis in clinical trials was 0.06% for both drugs[104] and transient changes in liver function tests have been noted in 1 in 100 to 1000 patients treated with ranitidine.[15] In a more recent report, the absolute risk of acute liver injury associated with cimetidine was slightly greater than 1 per 5000 users of cimetidine and the adjusted relative risk (compared to non-use) was 5.5. The adjusted relative risk for ranitidine was estimated to be 1.7.[105] It has been suggested that hepatotoxicity associated with cimetidine is almost always cholestatic whereas with ranitidine the reaction is more typically cholangitic with accompanying fever and chills. Studies using rat hepatocytes suggest that hepatotoxicity is greatest for ranitidine, followed by famotidine, then cimetidine.[106]

3.1.1 Cimetidine

In clinical trials, mild and usually transient elevations of liver enzyme and bilirubin levels did not occur more frequently in H_2 antagonist recipients than in the placebo recipients.[12,29] In 1 study, however, 4 patients had clinically significant rises in transaminase levels that returned to normal with continuation of therapy and in another 2 patients, liver biopsy revealed mild centrilobular necrosis.[29] Another patient developed liver damage that was thought to be associated with hypersensitivity.[26]

There have been a few reports of mild asymptomatic elevation in hepatic transaminase levels in association with H_2 antagonists, mostly in patients receiving high dosages of cimetidine.[10,11,107] In addition, modest increases in serum bilirubin levels with a marked rise in serum bile acid levels and normal transaminase levels were reported in 5 children.[108] This was interpreted as indicating that cimetidine interferes with bile secretion. There have been a few cases reported of acute hepatitis. Between 2 and 120 days after starting cimetidine, some patients developed a mixed-type hepatitis with a rash and fever and with recurrence on rechallenge.[25,109] Liver biopsy in 1 patient with cimetidine-induced hepatitis revealed centrilobular necrosis, bile stasis and mononuclear cell infiltration. Re-exposure to cimetidine caused a rapid rise in serum transaminase levels confirming the diagnosis in this case.[110] There have been 2 other reports where hepatitis recurred after rechallenge. In one case, febrile hepatitis followed 6 months of cimetidine and recurred on rechallenge 9 months later. Liver biopsy showed features consistent with chronic active hepatitis and antismooth muscle antibodies were positive however liver function normalised with a course of corticosteroid therapy and cessation of cimetidine.[111] In the second case, mild hepatitis occurred after 75 days of therapy and recurred within 5 days after deliberate rechallenge.[112] Liver biopsy revealed mild centrilobular necrosis with iron accumulation and cholestasis.

3.1.2 Ranitidine

As with cimetidine, transient increases in transaminase levels were noted during clinical trials with rantidine.[14,113] There have also been a few case reports of ranitidine associated with mild hepatitis. This resolved on withdrawal of the ranitidine[114-117] and in one case, despite continuation of therapy.[118] There have been 2 reports where mild hepatitis recurred on rechallenge. In one case liver biopsy showed mild bile stasis with modest intralobular infiltrates of lymphocytes, occasional aggregates of eosinophils and slight hepatocellular necrosis. Circulating ranitidine antibodies were not detected.[115] The second case showed focal hepatocellular necrosis on biopsy immediately following renal transplantation. Although there was a clear

temporal association between ranitidine and hepatotoxicity, the patient was taking multiple medications.[119] There has been another case reported where rechallenge was not associated with recurrence of abnormal transaminase levels.[120]

There has also been a report of severe hepatotoxicity with jaundice and relapse upon rechallenge.[121] In this case, biopsy revealed severe inflammation with lymphocytes, plasma cells, polymorphs and eosinophils in the infiltrate,[121] however, it was later suggested that the aetiology was post transfusion hepatitis.[122] In a second case, biopsy revealed granulomatous inflammation with eosinophilia.[116] Once again the causal association of ranitidine has been questioned.[123,124]

Cholestatic hepatitis with fever and chills has also been reported. This occurred in 3 patients between 3 and 5 weeks after starting ranitidine.[117] All 3 of these patients had received cimetidine previously for prolonged periods without any signs of hepatotoxicity. There are 3 other separate case reports of cholestasis following ranitidine. One case was associated with rash and hypereosinophilia,[125] another with myalgia and a mesenchymal reaction on liver biopsy,[126] and another case was protracted over 4 weeks despite corticosteroid therapy and liver biopsy showed diffuse panacinar canalicular cholestasis and cholestatic rosettes in zone 3.[127]

There have been an additional 6 cases of ranitidine-induced liver injury with subsequent complete clinical recovery and normalisation of liver function tests, reported to the Netherlands Centre for Monitoring of Adverse Reactions to Drugs.[128] One fatal case of ranitidine-induced hepatitis has been reported from France but the presence of antinuclear and antimuscle antibodies in this patient raised the possibility of autoimmune hepatitis.[129] Recently, a second case of fatal hepatic failure following 3 weeks of ranitidine therapy in a 66-year-old woman was reported.[130] In a recent review of ranitidine and hepatotoxicity it was concluded that there was often insufficient information to assess causality and many cases were confounded by concurrent factors that are associated with hepatotoxicity such as alcohol, use of other medications, blood transfusions or febrile illness.[127]

3.1.3 Famotidine

Hepatitis has been reported in 2 patients receiving famotidine. Interestingly, 1 patient developed another episode of hepatitis when she received cimetidine 1 month later,[131] while the other patient tolerated ranitidine but developed jaundice with famotidine.[132]

3.2 Australian Reports

A brief summary of cases of hepatotoxicity associated with H_2 antagonists reported to ADRAC is shown in table IV. In this series the onset of clinical symptoms and signs after exposure to H_2 antagonists varied from 1 day to 14 months. The clinical manifestations occurred within 1 month in 68% cases induced by cimetidine, in 69% of cases induced by ranitidine and 66% of cases induced by famotidine.

The majority of patients with hepatotoxic reactions were older than 50 years of age – 85% receiving cimetidine, 73% receiving ranitidine, and 77% receiving famotidine. The diagnosis of hepatitis induced by H_2 antagonists was based on clinical criteria including the temporal relationship between use of a drug and onset of liver abnormalities, exclusion of alternative causes of liver injury, and improvement after discontinuation of the drug. The diagnosis was proven by rechallenge in 3 patients receiving cimetidine.

Liver biopsy was performed on 15 patients with hepatitis (7 receiving cimetidine, 7 receiving ranitidine and 1 receiving famotidine). Pathology usually showed preservation of lobular architecture and mixed cholestasis (intracellular and intracanalicuar) with a mild nonspecific hepatic element. The portal tracts usually contained a mixed inflammatory cell infiltrate. In 3 patients receiving cimetidine granulomatous hepatitis was found. There was a tendency for the alkaline phosphatase level to be higher in the cimetidine group and for the alanine transaminase level to be highest in the ranitidine group. This suggests that a cholestatic picture might be more common in cimetidine-induced

Table IV. Summary of reports to Australian Adverse Drug Reactions Advisory Committee of hepatotoxicity associated with histamine H_2 receptor antagonist therapy

Parameter	Cimetidine (1976 to 1999)	Ranitidine (1980 to 1999)	Famotidine (1989 to 1999)
Total number of reported adverse reactions	716	1476	338
Number of reports of hepatotoxicity (% of total reports)	40 (6)	117 (8)	13 (4)
Mean age in years (range)	60.9 (19-84)	55.2 (17-96)	57.1 (24-81)
Gender (male : female)	2 : 3	1 : 1	1 : 1
Number of patients with jaundice (%)	10 (25)	60 (41)	4 (31)
Mean bilirubin level in mmol/L (range)	194 (45-504)	113 (26-478)	185 (60-384)
Mean ALP level in U/L (range)	485 (45-967)	395 (116-1809)	433 (116-1310)
Mean ALT level in U/L (range)	338 (58-1450)	487(44-4779)	513 (122-1318)
Mean GGT level in U/L (range)	464 (95-1474)	497 (42-2563)	488 (111-1174)
Biopsy proven	7	7	1
Number of patients with gynaecomastia (%)	80 (11.2)	33 (2.2)	14 (4.1)

ALP = alkaline phosphatase; **ALT** = alanine transferase; **GGT** = γ-glutamyl transferase.

hepatotoxicity compared with ranitidine where a hepatic profile may be more common.

Features suggestive of systemic hypersensitivity such as fatigue, pruritic maculopapular or erythematous rashes, leucocytosis, hypereosinophilia and elevated ESR were reported in 4 cases of cimetidine-induced hepatitis, 8 cases of ranitidine-induced hepatitis and in 1 patient taking famotidine. In 2 patients receiving ranitidine antinuclear antibodies were detected, suggesting autoimmune hepatitis. There were no fatalities. Improvement within 1 to 6 weeks after withdrawal of the drug was described in all cases.

3.3 Mechanisms

It has been suggested that H_2 antagonist–related hepatotoxicity is secondary to either metabolic idiosyncrasy or hypersensitivity reaction.[24,25,133,134] In fact, both mechanisms may be involved. In drug induced liver disease metabolic idiosyncrasy may be the initiating feature but immunological hypersensitivity is likely to be involved as an effector mechanism.[135]

A hypersensitivity mechanism appears more likely because: (i) the hepatitis is rare and unpredictable; (ii) there is no obvious dose-effect; (iii) the clinical and histopathological characteristics are consistent with hypersensitivity; and (iv) H_2 antagonists modulate the immune response through their effects on T lymphocytes. It is of interest that cimetidine significantly enhanced liver injury induced by delayed-type hypersensitivity to picryl chloride in mice.[136] H_2 antagonists have minimal effect on hepatic blood flow.[38,137]

On the other hand, H_2 antagonists or their metabolites may be directly hepatotoxic. Animal studies have shown that chronic administration of rantidine up to 100 mg/kg produces hepatotoxicity in a dose-related manner[115] although the relevance of these high doses in humans is unclear. Ranitidine is structurally based on a furan ring. Furans are hepatotoxic in the absence of an immune response and in a process which requires metabolic activation and glutathione depletion.[138] H_2 antagonists undergo cytochrome P450–mediated metabolism in the liver and it is possible that toxicity could be related to phenotypic or genotypic modulation of these pathways. However, blood concentrations of H_2 antagonists and their metabolites have not been reported in human cases of H_2 antagonist–associated hepatotoxicity.

4. Hepatitis and Acute Interstitial Nephritis

Of the 41 patients reviewed in this article with AIN (tables I and II), only 7 (17%) had a rise in alkaline phosphatase. In 1 case reported in the literature, the elevated alkaline phosphatase level

was associated with mild elevations of γ-glutamyl transferase and alanine transaminase.[49] In 9 reports of AIN submitted to the manufacturers, 8 were associated with elevated alkaline phosphatase levels.[49] An elevated alkaline phosphatase level does not necessarily indicate concomitant hepatotoxicity because this enzyme is found in many tissues. It has been suggested that the rise of alkaline phosphatase level often noted in cases of cimetidine-induced AIN may be of renal origin[46] and it has been speculated that this may have diagnostic significance.[49]

One case reported to ADRAC had evidence of both AIN and hepatotoxicity. This patient was a 40-year-old man who developed fever and myalgia 1 day after commencing cimetidine 400 mg/day. Three days after commencing cimetidine he was admitted to hospital with jaundice and oliguria. Investigations revealed elevated creatinine and liver enzyme and bilirubin levels (fig. 4), elevated ESR (111 mm/h) and normal eosinophil count. Renal biopsy revealed oedema of the interstitium, most marked in the juxtamedullary cortex, with an interstitial inflammatory infiltrate of histiocytes, lymphocytes and moderate numbers of eosinophils. Extension of the inflammation into the some tubules was noted focally. There were no granulomas, no tubular loss nor interstitial fibrosis. The renal arteries were normal. Immunofluorescence studies showed possible trace staining for IgA and complement C3 in mesangial areas. Electron microscopy showed that the glomeruli were normal. The nephritis and hepatitis had virtually resolved within 1 week of ceasing cimetidine. Such a clinical picture has not been described previously.

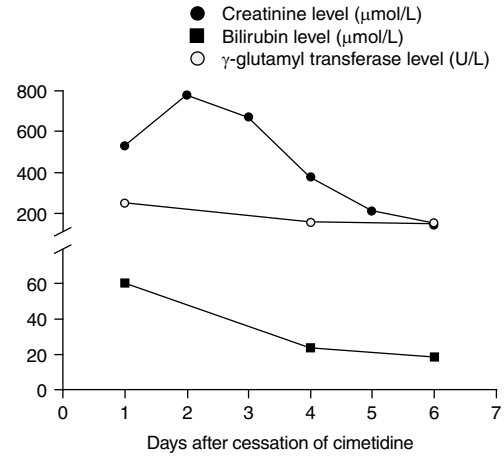

Fig. 4. Clinical course of a patient whose details were recorded in the Australian Adverse Reaction Advisory Committee database who experienced both hepatotoxicity and acute interstitial nephritis after receiving treatment with cimetidine.

5. Conclusions

Hepatotoxicity and AIN secondary to H_2 antagonist therapy are very rare. Furthermore, ascertainment of causality is difficult and could only be considered certain in the few cases where there was a positive rechallenge in the absence of confounding factors. Often the diagnosis of an adverse drug effect is only based on evidence such as the temporal association between the medication and adverse effect, characteristic clinical and pathological findings and exclusion of other diagnoses.

Both hepatotoxicity and nephrotoxicity were reported more frequently in older people. Unlike the clinical picture associated with other drugs, H_2 antagonist–induced AIN tends not to be associated with rash, arthralgias and flank pain. Eosinophiluria and elevated alkaline phosphatase levels are not reliable markers of H_2 antagonist–induced AIN. Invariably, renal failure resolves quickly after cessation of therapy and recurs after re-exposure to the same drug, but may not recur upon exposure to a different H_2 antagonist. However, there do not appear to be any major differences in the features of AIN associated with the different H_2 antagonists and the mechanism may be at least partially related to the pharmacological effect of H_2 antagonists on T lymphocyte function. This suggests that AIN may be a class effect of all H_2 antagonists. Hepatotoxicity is less well understood or described. It occurs with all H_2 antagonists and includes both hepatic and cholestatic features. Although these adverse effects are very rare, they can produce considerable morbidity. Now that many H_2 antagonists are available over-the-counter, awareness of these conditions and

early detection with cessation of H_2 antagonists therapy would appear to be paramount.

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