NSAIDs: RANKING ON BASIS OF ADVERSE REACTIONS AND DEATHS PER MILLION PRESCRIPTIONS

Serious gastrointestinal		Total serious		Deaths	
Drug	Rate	Drug	Rate	Drug	Rate
*Azapropazone	67·0	*Azapropazone	87·9	*Azapropazone	9·9
*Piroxicam	58·7	*Fenbufen	69·4	*Fenoprofen	6·6
*Fenbufen	35·7	*Piroxicam	68·1	*Piroxicam	6·2
*Diflunisal	33·5	*Sulindac	54·3	*Naproxen	5·6
Ketoprofen	33·2	*Diflunisal	47·2	*Sulindac	5·1
*Naproxen	32·8	Fenoprofen	43·7	*Fenbufen	4·5
Fenoprofen	32·3	*Naproxen	41·1	*Diflunisal	3·5
Flurbiprofen	27·4	Diclofenac	39·4	Flurbiprofen	3·3
*Sulindac	23·9	Ketoprofen	38·6	Diclofenac	3·1
Diclofenac	20·9	Flurbiprofen	35·8	Ketoprofen	1·6
Ibuprofen	6·6	Ibuprofen	13·2	Ibuprofen	0·7

*Long plasma half-life.

the *Drugs and Therapeutics Bulletin* did not mention this factor. A reworking of Committee on Safety of Medicines (CSM) adverse reactions data[2] for the eleven NSAIDs currently used in the UK and covered in that article suggests that the toxicity of an NSAID and its plasma half-life are related.

The accompanying table lists the eleven drugs in descending order of toxicity. The drugs are classed as of long half-life if they or their active metabolites have half-lives of 10 h or more; the other five compounds all have short half-lives, of 4 h or less. This analysis reveals a preponderance of drugs of long half-life drugs at the top of the ranking order. Indeed, fenoprofen apart, there is a complete polarisation for all serious adverse reactions and for drug-associated deaths.

Adverse reaction data based on the UK's voluntary yellow-card reporting system are imperfect and the CSM lists some of the potential confounding factors.[2] Nevertheless, I feel that the table does demonstrate that NSAIDs with long half-lives are more likely to produce serious adverse reactions and that much greater consideration should be given to plasma half-life when deciding which NSAID to prescribe. That half-life is not the only factor in NSAID toxicity is shown by the fact that several with a short half-life have lately been withdrawn. The adverse reactions of NSAIDs are related not only to their ability to inhibit prostaglandin synthesis (and hence gastric mucosal and renal blood flow) but also to the chemical and physicochemical properties of the individual molecules. Whichever factors are involved it is likely that high and prolonged blood levels will exacerbate any toxic effects.

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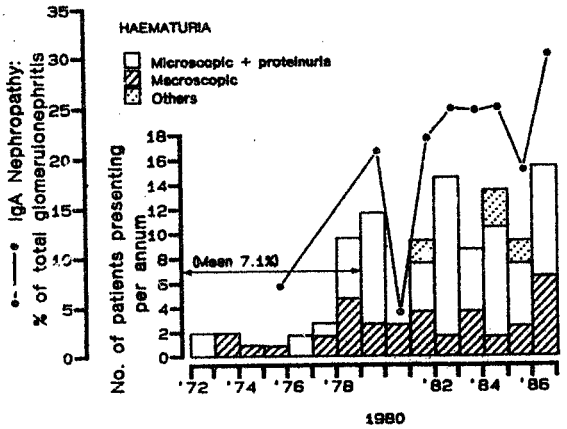
INCREASING FREQUENCY OF ADULT IgA NEPHROPATHY IN THE UK?

SIR,—IgA nephropathy is a prevalent infection-associated glomerular disease in developed countries, and a significant cause of progressive renal failure. There is striking variation worldwide in the reported frequency of the disease.[1] Detection of the nephropathy in 43·3% of renal biopsies for primary glomerular disease in Japan[2] contrasts with its apparent rarity in the USA and UK. An early study in the UK reported a frequency of 4% (1976),[3] and a figure of 10% is recorded by the MRC Glomerulonephritis Registry (1984).[4] An apparently anomalous report of 21·8% of primary glomerulopathies in north-east Scotland in 1977–80[5] has not yet been confirmed in other regions in the UK. We have reviewed the numbers and clinical features of adult patients diagnosed with IgA nephropathy in a single centre, Manchester Royal Infirmary, for the fifteen-year period 1972–86.

For the period to end-1978, IgA nephropathy was detected in 7·1% of biopsies showing glomerular disease, whereas the frequency for 1979 to end-1986 was 21·1%. During 1986, the diagnosis was made in 31% of glomerulopathies (figure). This apparent increase is predominantly a result of an increase in the absolute numbers of patients with IgA nephropathy presenting with microscopic haematuria and proteinuria, with little change in



IgA nephropathy in adults, Manchester Royal Infirmary 1972–86.

the incidence of those with episodic macroscopic haematuria.

These findings substantially support the suggestion[5] that IgA nephropathy is not rare in the UK. The true disease incidence may be greater than previously suspected, and comparable with that in countries reporting the highest detection rates. The rise in apparent incidence is largely due to increased number of patients with microscopic haematuria, and may reflect changes in frequency of detection rather than a true rise in incidence. Changing referral patterns and attitudes towards biopsy for adults presenting with minor urinary abnormalities are more likely explanations than more stable influences within a population, such as its genetic composition. We are now reviewing the policies in UK centres for investigation of patients with haematuria to establish the nature and extent of variability in nephrological practice which might influence the apparent incidence of IgA nephropathy.

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FULL-SPECTRUM CLASSROOM LIGHT AND SICKNESS IN PUPILS

SIR,—The number of days children at Green Street Elementary School, Brattleboro, Vermont, were off sick fell significantly after distorted spectrum fluorescent (DSF) light was replaced by full-spectrum fluorescent (FSF) light.

As an experiment the DSF light in three classrooms at this school, where pupils are 5–9 years old, was replaced by FSF light ('Vitalite') during the holiday in December, 1986. The three classrooms were chosen by the school's principal (with the consent of the teachers) primarily because the rooms were on different sides of the building. At the end of the school year I tabulated from the attendance records of the school the total number of daily absences due to sickness (as opposed to family holidays and other reasons unrelated to illness) during September, October, November, and December, 1986 (70 days of school), and from January to the end of June, 1987 (105 days), when the FSF light was in place. The table shows the sickness rates for the three classrooms that had FSF light, for all other classrooms in the school, and for three classrooms without FSF light paired, for grade, with the three experimental classrooms.

SICK DAYS IN GREEN STREET ELEMENTARY SCHOOL, 1986–87

Rooms (no of pupils)	No of sick days (and average per pupil per 100 days)		p*
	September–December	January–June	
FSF light (61)	98 (2·30)	140 (2·19)	NS
Rest of school (192)	313 (2·33)	578 (2·87)	<0·01
Three paired rooms (60)	108 (2·57)	209 (3·32)	<0·05
p*,†	NS (NS)	<0·01 (<0·001)	

*Statistical comparisons between the number of sick days are by χ^2 test with one degree of freedom.
†For FSF light *vs* rest of school (and *vs* three paired rooms).

In the term before the FSF light was introduced the sickness rate in the FSF designated classrooms was not significantly different from that in the rest of the school or in three paired classrooms. Thus there was no evidence that students in the experimental rooms started off any healthier than the other children. When the FSF light was in place, the sickness rate in the experimental classrooms was lower than that in the rest of the school and in the three paired classrooms (table). The effect was to reverse the usual seasonal pattern in the school wherein sickness absences increase during the winter and spring months. In classrooms without FSF light the rate of sick days increased significantly from September–December to January–June period but in the FSF light classrooms the sickness rate fell slightly.

This study was not blind but neither the pupils nor the staff expected that FSF light might affect sickness absence, and nor did I. DSF light raises the serum cortisol level[1] more than FSF light does,[2] and glucocorticoids suppress cell-mediated immunity.[3] Perhaps FSF light, which is used to treat the seasonal affective disorder,[4] may also be useful in the treatment of immune disorders.

The teachers found the FSF light brighter, more natural, and more pleasant, and they tended to keep it on for longer and did not wish to return to the DSF light.

I thank Mr Robert Neubauer, principal, and Mrs Marie Tatro, secretary, of the Green Street Elementary School.

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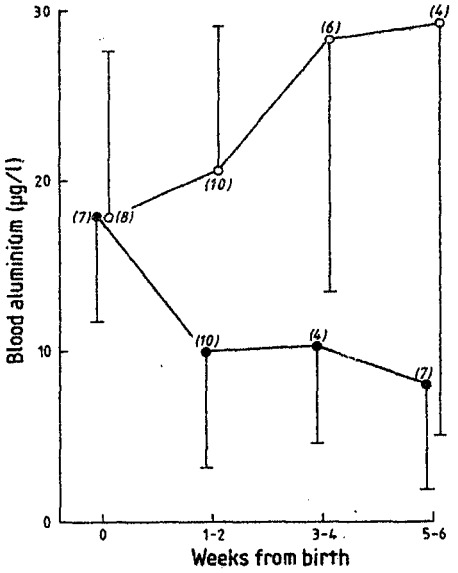
BLOOD ALUMINIUM LEVELS IN PRETERM INFANTS FED PARENTERALLY OR WITH COWS' MILK FORMULAE

SIR,—We[1] and others[2] have reported widely variable aluminium levels in milk and parenterally administered solutions. Preterm infants, who have poorer renal function, are at risk of the toxic effects of excess aluminium retention, including encephalopathy.[3] Between April and November, 1986, 56 blood samples were collected from 22 preterm infants (24–32 weeks' gestation). Blood was withdrawn into aluminium-free bottles via stainless steel needles, and samples were analysed in a single batch by graphite-furnace, atomic absorption spectroscopy. The infants were divided into two groups: group A was fed parenterally and group B was fed standard cows' milk formulae, although some in group B initially received glucose and electrolyte infusion.

Mean whole-blood aluminium levels are shown in the figure. At birth mean aluminium levels were similar in the two groups, as expected (about 18 µg/l). There were significant differences in whole-blood aluminium levels at weeks' 1–2, 3–4, and 5–6. No patient received parenteral nutrition for more than 6 weeks.

Blood aluminium levels of bottle-fed babies fell over the 6-week period, approaching values previously obtained in term infants (2·0–10·0 µg/l).[3] Mean blood levels in parenterally fed infants increased over the first 2 weeks to reach a plateau at about 28 µg/l



Mean (SD) whole-blood aluminium in preterm infants.

○ = group A, fed parenterally; ● = group B, fed standard cows' milk formulae. Figure in parenthesis = number of samples. Significant difference between the groups at weeks 1–2 ($p < 0·01$), 3–4, and 5–6 ($p < 0·05$, Wilcoxon rank-sum test).

(range over weeks 3–6 was 9–65 µg/l). In adults with advanced renal disease blood levels of over 50 µg/l have been associated with osteodystrophy and encephalopathy.[4] The effects of serum aluminium concentrations approaching this level in preterm infants with a high bone turnover and a developing nervous system are unknown. Brain aluminium concentrations are increased in neonatal uraemia.[5]

Our two groups were not strictly comparable: the parenterally fed babies were more preterm (mean 28·1 *vs* 30·5 weeks) and lighter at birth (1136 g *vs* 1465 g) than those fed enterally. The two groups were not fed similar quantities of aluminium: group A received a mean of 17·6 µg/kg per day (range 0·8–38·8) whereas group B received 47·8 µg/kg per day (17·0–59·2). Consequently we do not know whether the blood levels reflect changes in aluminium absorption or excretion, and longitudinal studies are in progress.

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HOW LIQUORICE WORKS

SIR,—Dr Stewart and his colleagues (Oct 10, p 821) postulated that liquorice acts by inhibiting 11β-hydroxysteroid dehydrogenase (11β-OHSD), a microsomal enzyme complex which catalyses the reversible conversion of mineralocorticoid active cortisol to mineralocorticoid inactive cortisone. It is suggested that raised intrarenal cortisol levels saturate renal extravascular cortisol-binding globulin, leaving cortisol to act on the mineralocorticoid receptor. If so one would expect anyone consuming liquorice to be