into fine powders and stuck to SEM stubs, coated with carbon, and examined in the SEM. The main constituents of the pigments were as follows. Red: sulphur, silicon, aluminium, and chlorine; green: titanium, silicon, and copper; white: titanium, aluminium, zinc, calcium, and silicon; orange: titanium and chlorine.

Discussion

The development of granulomatous hypersensitivity to a constituent of the red pigment used in tattoos is well documented.[2] Apparently mercuric sulphide is often the agent responsible.[2] Nevertheless, mercury now seems to be an infrequently used tattoo pigment.[3]

We can find no previous report of the dramatic lichenoid response seen in our patients. The resemblance to lichen planus was emphasised by the striking immunofluorescence findings, which included a fibrin band and strongly fluorescent cytoid bodies with most of the reagents tested.[4] Clearly, three of the patients (cases 1, 2, and 4) did not have lichen planus (or lupus erythematosus) as there were no other lesions on the skin or mucosae. The solitary tattoo reaction in case 3 was identical with that in the other three patients clinically, histologically, and on direct immunofluorescence. Nevertheless, this patient had had discoid lupus erythematosus with lichenoid features. His reaction was not merely a local expression of his lupus erythematosus induced by the trauma of tattooing as it was confined to the red portion of one tattoo. The relation between this patient's condition and his odd lichenoid reaction must remain doubtful.

These four patients presented within six months of each other, and the consistent presence of the unusual lichenoid response in all the patients' lesions surely could not have been coincidental. Scutt[3] stated that no more than 10 patients with tattoo granulomata are seen yearly in the United Kingdom. The question therefore arises whether the tattooist had inadvertently included some other substance in the injected material.

Electron-probe microanalysis showed mercury in the dermis in only one section, but the amount detected was small and could have been a "contaminant." Mercury hypersensitivity on patch testing was found in only one patient (case 1). The red pigment we obtained contained no mercury. The negative patch test results in the other three patients did not necessarily mean that they were not hypersensitive to injected mercury, as their hypersensitivity had been provoked by intracutaneous injection and not epicutaneous challenge.

The lesions of lichen planus may be associated with immune reactions.[5] Possibly in our patients the local antigenic challenge supplied by the unknown constituent of the tattoo pigment induced a local immunological response resulting in true lichen planus. Or perhaps these patients had been inoculated with an infectious agent which caused the local tissue reaction. If this was the case it has intriguing implications for the possible aetiology of spontaneously occurring lichen planus.

We thank Mr Nick Moore, department of crystallography, Birkbeck College, London, for help with the electron-probe microanalyser.

References

[1] Beutner, E H, Chorzelski, T P, and Jordan, R E, *Autosensitization in Pemphigus and Bullous Pemphigoid.* Springfield, Illinois, Charles C Thomas, 1970.
[2] Scutt, R M, and Gotch, C, *Skin Deep: the Mystery of Tattooing*, p 133. London, Peter Davies, 1974.
[3] Scutt, R M, *British Journal of Hospital Medicine*, 1972, **8**, 194.
[4] Abell, E, *et al*, *British Journal of Dermatology*, 1975, **93**, 17.
[5] Davies, M, *et al*, *British Journal of Dermatology*, 1977, **96**, 145.

(*Accepted 30 December 1977*)

SIDE EFFECTS OF DRUGS

Incidence of thrombophlebitis with naftidrofuryl

Woodhouse and Eadie[1] recently reported an unusually high incidence of thrombophlebitic complications with intravenous infusions of naftidrofuryl (Praxilene), a drug widely used for treating vascular insufficiency. They described 13 naftidrofuryl infusions (200 mg naftidrofuryl in 200 ml dextrose or common salt solution twice daily) given to seven elderly patients, severe rapidly progressing thrombophlebitis being observed on 10 occasions. Other observers[2 3] disagreed with this experience and reported a low incidence of thrombophlebitis when the drug was given in a dose of 200 mg diluted in 500 ml of dextrose.

Survey and results

To determine the frequency of thrombophlebitic complications from the use of naftidrofuryl infusions in Germany we approached 13 angiological centres for information on their experiences with the drug. The results (see table) showed that the incidence of thrombophlebitis in patients given

Details of naftidrofuryl infusions used in 13 centres in Germany and incidence of thrombophlebitis*

Centre	No of infusions	Period of use (years)	Average dose per infusion (mg)	Average duration of infusion (hours)	Basic solution used	Incidence of thrombophlebitis
1	15 000	8	800–1600	2–3	500 ml physiological NaCl	Extremely seldom. No serious or ascending thromboses
2	7 250	5	400–1200	2–4	NaCl	None
3	15 500	6	600–1000	1–3	Rheomacrodex or physiological NaCl	So far about 15 episodes; connection with infusions not certain
4	4 680	6	400	2	500 ml 5% glucose	None
5	11 760	6	200–400	1–2	500 ml physiological NaCl or 500 ml 5% fructose	About 2·8%
6	20 250	8	120–400	—	500 ml NaCl	No obvious association between thrombosis and infusions
7	8 500	7	200–800	—	500 ml 5% fructose	About 0·5%
8	18 000	5	400–1400	2–4	Physiological NaCl	Less than the usual risk of thrombophlebitis
9	8 000	8	≤2000	—	Physiological NaCl	None
10	11 750	4	400	1½–2½	500 ml physiological NaCl	Local reactions only
11	3 500	4	≤1200	4	500 ml physiological NaCl	About 0·5%
12	15 000	5	400	1½–2	—	Normal complication rate (3%)
13	20 000	7	≤1600	—	—	Only three clear cases of thrombosis associated with infusion

*Details of the centres listed may be obtained from the author.

naftidrofuryl corresponds to that found with other intravenous infusions and is below the 12–30% quoted as normal by Woodhouse and Eadie.[1] The sporadic cases of phlebitis observed were not particularly severe and central venous complications did not occur.

Comment

Reports of the side effects of commonly used drugs are essential for assessing their therapeutic value, but they need independent confirmation. The observations of Woodhouse and Eadie[1] have not been confirmed. There is no justification for a general warning that the infusion of naftidrofuryl is associated with a high incidence of thrombophlebitis.[4]

[1] Woodhouse, C R J, and Eadie, D G A, *British Medical Journal*, 1977, **1**, 1320.
[2] Chamberlain, J, *British Medical Journal*, 1977, **2**, 121.
[3] Morris-Jones, W, *British Medical Journal*, 1977, **2**, 122.
[4] *Arznei-Telegramm*, 1977, **7**, 60.

(*Accepted 8 December 1977*)

Kardiologische Abteilung, Medizinische Klinik und Poliklinik der Freien Universität Berlin, Klinikum Charlottenburg, Spandauer Damm 130, 1000 Berlin 19, Germany

H HEIDRICH, MD, privatdozent and assistant professor

Ibuprofen hypersensitivity in systemic lupus erythematosus

The anti-inflammatory agent ibuprofen is widely used in rheumatoid arthritis. The drug has also been used in treating systemic lupus erythematosus (SLE), and hypersensitivity reactions associated with such treatment have been reported. We describe two further cases and review five cases reported elsewhere.

Case reports

Case 6—A 54-year-old woman with SLE of three years' duration had been given ibuprofen 400 mg three times daily for a month. Ten days after treatment started she developed a generalised erythematous rash and high fever which did not respond to antipyretics. She stopped taking ibuprofen and the fever and rash subsided. A few days later she was again treated with ibuprofen because of arthralgia. A few hours after the first tablet she again developed a high fever and erythematous rash but with vomiting and abdominal pain, which continued for three days. She was admitted to hospital and all medication was stopped. Her temperature was 39°C but fell to normal the following day; no other physical abnormality was found. ESR was 75 mm in first hour, antinuclear factor was present at high titres, and lupus erythematosus cells were detected. The latex fixation test was positive 1/16 and serum complement was at the lower limit of normal. On admission the serum alkaline phosphatase was 155 U (normal up to 80 U), serum alanine aminotransferase (SGPT) 255 U (normal up to 40 U), and serum aspartate aminotransferase (SGOT) 105 U (normal up to 40 U), but all returned to normal within six days. On the eighth day in hospital, the patient developed migratory joint pains, and she was again given ibuprofen. Two hours after the first tablet her temperature rose to 39·2°C and she developed nausea, vomiting, abdominal pain, and a generalised erythematous rash. Ibuprofen-induced reaction was considered and the drug discontinued. Twenty-four hours later liver function values were again abnormal: alkaline phosphatase 210 U, SGOT 105 U, and SGPT 200 U. Liver biopsy two days after the onset of the above reaction showed minimal fatty changes only. The patient was started on chloroquine (Aralen) 250 mg/day, and discharged a few days later feeling well. Three months later she was well and no further episodes of fever or rash had occurred.

Case 7—A 15-year-old girl with suspected rheumatoid arthritis was treated with aurothioglucose (Solganal) once a week and ibuprofen 1200 mg daily. Six days later she was admitted to hospital with a temperature of 39·3°C, abdominal pain, vomiting, and headache. She had a generalised macular rash and SGOT rose to 185 U. A hypersensitivity reaction to ibuprofen was considered and the drug stopped. Twenty-four hours later her temperature fell to normal and the rash disappeared. Two months later the patient was readmitted because of arthritis, a butterfly rash, and severe weight loss, and laboratory studies and renal biopsy showed evidence of SLE.

Discussion

Ibuprofen is generally well tolerated and is most commonly used in treating rheumatoid arthritis and degenerative joint disease. But its use in treating the arthralgia of SLE is not widely accepted. We found reports of five patients with SLE who developed hypersensitivity reactions to ibuprofen.[1–3] Clinical and laboratory findings for these patients and our two patients are given in the table. Of the seven patients, five received ibuprofen alone and developed fever and gastrointestinal side effects. The two other patients were given steroids in addition to ibuprofen, which resulted in a rash or abdominal pain without fever.[3] These patients were part of a series of 17 patients with SLE and all received steroids as well as ibuprofen. We have treated two patients with SLE with steroids, also without any untoward reaction. Treatment with steroids may wholly or partly prevent the hypersensitivity reaction to ibuprofen in such patients.

Four patients developed a rash. This reaction is uncommon in patients with rheumatoid arthritis receiving ibuprofen,[4–6] though in some patients it has been associated with fever.[7] In patients with rheumatoid arthritis, gastrointestinal disturbances were the most common side effect of ibuprofen, with an incidence of 10-30%.[8] Raised concentrations of serum transaminases and alkaline phosphatase have been noted occasionally during ibuprofen treatment,[9–11] and there is one reported case of hepatic damage with jaundice.[12] Studies on the toxicity of ibuprofen in animals showed that plasma transaminase activity was normal[13] and histological signs of liver damage were absent. A transient enlargement of the liver was the only finding in rats receiving very high doses (180 mg/kg/day) of the drug.

In our two patients and four of the five review cases the manifestations of hypersensitivity involved the gastrointestinal tract, and in four the concentrations of serum transaminases were raised. In our first patient liver biopsy showed only slight fatty changes. This is well recognised in SLE and is not, we believe, related to treatment with ibuprofen. One patient (case 3) died after treatment with ibuprofen, and fatty metamorphosis of the liver was found at necropsy. Raised concentrations of serum transaminases also seem to be common in patients with active SLE who are receiving aspirin.[14] The hepatotoxic effect of aspirin in these patients may be due not to an allergic reaction but to a disturbance in aspirin metabolism, resulting in the formation of a toxic metabolite. It is speculative whether the same mechanism is found in patients with SLE receiving ibuprofen and whether the fatty metamorphosis of liver in the third patient was due to this hepatotoxic effect. Nevertheless, the raised concentrations of serum transaminases in the other three patients may have been a manifestation of an allergic reaction, since they also had symptoms and signs of a generalised hypersensitivity reaction.

Thus ibuprofen should be considered as a possible cause of abnormal

Clinical and laboratory findings in seven patients with systemic lupus erythematosus treated with ibuprofen alone or ibuprofen and steroids

Case No	Treatment		Symptoms				Laboratory findings		References
	Ibuprofen alone	Ibuprofen and steroids	Fever	Rash	Nausea or vomiting	Abdominal pain	SGOT (U)	Liver biopsy	
1	+		+		+	+	147		Mandell *et al*[1]
2	+		+			+			Mandell *et al*[1]
3	+		+	+	+		6200	Fatty metamorphosis of liver	Bravo *et al*[2]
4		+		+					Dubois[3]
5		+				+			Dubois[3]
6	+		+	+	+	+	105	Slightly fatty liver	Present series
7	+		+	+	+	+	185		Present series

SGOT = Serum aspartate aminotransferase.