metabolism in the liver is unknown.[9] The pharmacokinetics of disulfiram have not been elucidated because there are no sensitive and specific methods of determining disulfiram and its metabolites.

Acute toxicity studies with disulfiram in rats have shown no signs of liver necrosis but disulfiram decreases the drug metabolising capacity of the liver.[10 11] This mechanism probably accounts for disulfiram's inhibition of diphenylhydantoin and warfarin metabolism.[12 13]

Our findings indicate that long-term toxicity studies in animals should be performed to detect possible hepatic damage after pro-prolonged administration of disulfiram.

We thank Dr K Winkler for allowing us to report observations in case 1.

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Photo-onycholysis caused by demethylchlortetracycline

Photodermatitis is a well-known and relatively common side effect of treatment with the tetracyclines. It appears as a bright erythema of the exposed skin in response to sunlight. Photo-onycholysis is another recognised side effect of the tetracyclines but is much less common and less widely known.

Case report

A 64-year-old housewife was treated for a chest infection with demethylchlortetracycline (demeclocycline), 150 mg four times a day, from 4 August 1976. On 5 August 1976 she spent about two and a half hours in the sun. By that evening she had developed severe erythema and blistering of the face, arms, and legs where her skin had been exposed. The eruption got worse over the next 24 hours. She was treated with oral antihistamines and topical corticosteroids and it took three weeks for her skin to return to normal.

On 9 September 1976, five weeks after the onset of the rash, she developed onycholysis of two nails of the right hand. By 6 October 1976 the onycholysis affected all the finger nails: the distal two-thirds of most nails had separated from the nail beds. Thereafter there was a steady improvement, though the nails did not return to normal until mid-March 1977.

Comment

Photo-onycholysis may occur with tetracycline[1] and doxycycline[2] as well as with demethylchlortetracycline. Usually it accompanies a severe photodermatitis but it is occasionally seen when the skin is not otherwise affected. It is a rare side effect in Britain and has not been reported from the UK. From March 1964 to December 1975 the Committee on Safety of Medicines was notified of 91 cases of photosensitive eruptions due to demethylchlortetracycline treatment but only one case of unspecified "nail disorder."[3] Reports of photo-onycholysis have all come from countries with hotter climates, such as India,[1] Spain,[4] and the USA.[5] If, however, the weather we experienced in the UK last year sets a precedent for the future it would be wise to avoid prescribing demethylchlortetracycline in the summer. This drug should also not be given to patients about to holiday abroad in the sun.

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Convulsive seizures and viloxazine

Viloxazine is a novel bicyclic compound with atypical pharmacological properties. It is marketed as the antidepressant Vivalan. During a trial of this drug—a double-blind comparison with placebo—one of the patients treated with viloxazine had three convulsive seizures. This was an unexpected finding because viloxazine protects rodents from convulsions induced electrically and with pentylenetetrazole,[1] these tests being indicative of potential anticonvulsant activity in man.

Case report

The patient was a 50-year-old man with depressive psychosis. He had no family or personal history of a neurological disorder and no signs of a concomitant physical illness. He had not abused alcohol, barbiturates, or other drugs.

On the sixth day of treatment with viloxazine, 100 mg three times a day, he said that he felt lost and that he did not know where he was. Shortly afterwards he complained of headache. Three-quarters of an hour later he fell to the ground and had a typical grand mal attack with generalised convulsions. On recovery he was disorientated in time and place, and he claimed that the staff were trying to make him mad. It was thought that he was in a postictal confusional state. Viloxazine was discontinued. Several hours later he had two more grand mal seizures. Examinations after each attack showed no abnormal physical signs. His persecutory ideas persisted for a few days.

The following values, measured during the trial, were all normal: haemoglobin; total and differential white blood cell count; erythrocyte sedimentation rate; blood sugar; glucose tolerance; and serum protein, albumin, calcium, inorganic phosphates, cholesterol, urea, creatinine, total bilirubin, alkaline phosphatase, lactic dehydrogenase, and aspartate aminotransferase. Chest and skull radiographs were also normal. An electroencephalogram, recorded 11 days after the fits, showed a mild, non-specific abnormality with generalised theta activity, but no focal or paroxysmal features.

The patient was followed up for four years. During this time he remained free from further attacks and symptoms and signs suggestive of an insidiously developing neurological disorder.

Comment

The difficulties of establishing a cause-and-effect relation between the administration of a drug and the occurrence of an unwanted effect are well known. It is equally well known that no firm conclusions can be drawn from a single case report. The only other possible cause of the fits was withdrawal of the therapeutic doses of benzodiazepines that his general practitioner had prescribed for him up to three days before his inclusion in the trial. The patient had received chlordiazepoxide 10 mg three times a day and nitrazepam 5-10 mg at night for

four days and, before this, diazepam 5-10 mg thrice daily and nitrazepam 5 mg at night for seven months. Although fits may occur when larger doses of benzodiazepines are withdrawn, their occurrence after withdrawal of therapeutic doses of this kind is extremely rare.[2]

A review of published reports has shown only one other case of fits possibly induced by viloxazine; this also occurred during a clinical trial.[3] In this study a second patient also had an epileptic seizure but was already known to be epileptic. By contrast, Brion[4] found no increase in the frequency of fits among the four depressed epileptic patients included in his trial.

Several psychotropic drugs, including tricyclic antidepressants and monoamine oxidase inhibitors, can precipitate grand mal seizures in people with low convulsive thresholds due to genetic susceptibility or previous brain damage, so it is essential to carry out electroencephalographic studies during the early clinical evaluation of new psychotropic drugs. In the case of viloxazine these were carried out by Pichot *et al*[5] and Floru *et al*[6] during the course of their double-blind comparisons with imipramine. The incidence of abnormal tracings was similar for both drugs.

Although a causal connection between viloxazine and convulsive seizures cannot be established with certainty, this case suggests the possibility that viloxazine has epileptogenic properties. I hope that any other cases of seizures occurring in patients receiving this drug will be reported.

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Dysarthria: an unusual side effect of tricyclic antidepressants

The dibenzazepine derivatives, which include amitriptyline and imipramine, are the most widely used drugs for treating depression. Although the postulated action of tricyclic antidepressants is thought to be related to the inhibition of biogenic amine reuptake, little is known about the mechanism of action of these drugs. Their efficacy in alleviating depression has, however, been well established.

The most commonly encountered side effects of the tricyclic drugs are those attributable to atropine-like action, including dry mouth, constipation, tremor, dizziness, tachycardia, blurred vision, and urinary retention. Various cardiovascular effects including changes in the electrocardiogram have also been recorded.[1] A dyskinetic syndrome occurring during administration of tricyclic antidepressants has also been observed.[2] I report here the development of dysarthria on tricyclic treatment.

Case reports

Case 1—A 42-year-old woman was admitted for the first time with a primary diagnosis of depression with anxiety. On admission physical and biochemical investigations showed nothing abnormal. Treatment with dothiepin (thioanalogue of amitriptyline) 25 mg three times a day was started. On the third day the patient reported difficulty with her speech. Continued treatment and observation for the next two days failed to clear the symptoms. Two days after dothiepin was withdrawn her speech returned to normal.

Case 2—A 48-year-old woman was admitted with agitated depression. Amitriptyline 25 mg three times a day was started. The dose was increased to 50 mg three times a day on the third day. A day later she reported speech difficulty. Observation for the next two days confirmed the nature of the symptom. Withdrawal of treatment resulted in the establishment of normal speech.

In neither case was adjunct therapy prescribed.

Comment

Both patients presented with considerable speech difficulty, which could best be described as a "stutter." On examination it became apparent that this dysfunction was a dysarthria resulting in a failure of proper articulation of the labials, the linguals, and the palatal consonants, which were all affected to an equal extent. The speech was characteristic of scanning speech as is often observed in patients with lesions affecting the cerebellum but distinguished from it by an absence of facial grimacing and explosive speech.[3]

In view of the patients' acute embarrassment at their speech difficulties continued treatment with tricyclic drugs was not thought to be justified, and total withdrawal of the drugs produced complete amelioration of symptoms.

Some investigators[4 5] have suggested that depressive states may be related to excess cholinergic activity in the brain and that amitriptyline and similar compounds produce their effects by virtue of their anticholinergic action. While the data on the incidence of side effects of antidepressants are by no means comprehensive, amitriptyline does seem to produce more anticholinergic side effects than other drugs.[6] Although the number of patients affected was small, the appearance of speech difficulty at therapeutic doses range (75-225 mg) is significant.

These two cases illustrate a hitherto unrecognised side effect of tricyclic therapy. It is suggested that the dysarthria may be produced by the direct anticholinergic effect of the tricyclic drug on the cerebellar connections and the striatum, leading to a selective incoordination of articulation.

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