Adverse drug reaction of the month

Risperidone-induced photosensitivity

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Adverse drug reactions present in a variety of ways, and can mimic any disease. Drug toxicity should be considered early on in the differential diagnosis of a patient's illness, particularly when a clear history is unavailable. We report the case of a serious reaction to a relatively new antipsychotic drug in an educationally subnormal patient.

Adverse drug reaction report

A 69-year-old woman with a history of learning difficulties, epilepsy and schizophrenia, who was in long-term institutional care, was admitted in mid-summer with a one-day history of rash, palpitations, and feeling generally unwell. The rash was erythematous with areas of blistering and early desquamation, and was most pronounced in the areas of sun exposure, although there was spread beyond the exposed areas. On admission, the patient was on sodium valproate (1 g/day), procyclidine (10 mg/day), risperidone (4 mg/day), ibuprofen (800 mg at night) and lofepramine (70 mg at night). The patient had been on all these drugs for a number of years, apart from risperidone, which had been started four months prior to admission. She had not used any new topical applications nor did she use cosmetic preparations. On examination, the patient was clinically dehydrated, and had a temperature of 35.1°C. The pulse rate was 130 beats/min and blood pressure was 70/50 mmHg. The patient was not acutely psychotic on admission.

The electrocardiogram (ECG) on admission showed the patient to be in atrial flutter with variable block (ventricular rate of 143 beats/min). Renal function was also abnormal (urea 20.6 mmol/l, creatinine 241 µmol/l). The patient was treated with intravenous fluids, digoxin and subcutaneous heparin as well as topical clobetasone and miconazole. Secondary bacterial infection of the skin was treated with intravenous penicillin and flucloxacillin. Apart from sodium valproate, all the other medications were stopped.

Following drug withdrawal and symptomatic therapy, the patient recovered quickly with a resolution of the skin rash. The biochemistry returned to normal and ECG prior to discharge showed controlled atrial fibrillation. Autoantibody screen and thyroid function tests were normal, and porphyria was excluded.

On day 11, the patient was tested for evidence of photosensitivity. The patient's responses to dose-ranges of ultraviolet (UV)B (290-320 nm) and UVA (320-400 nm) were determined on the skin of the back using a

xenon arc light source with monochromator (High Intensity Monochromatic System, LOT-Oriel Ltd, Surrey, UK). The erythematous threshold dose (minimal erythematous dose, MED) for each wavelength tested was noted at 24 hours post-irradiation, and compared with the normal range. Consistent with a drug photosensitivity reaction, reduced MEDs were observed to wavelengths of light within the UVA spectrum (table). Normal erythematous responses were seen to UVB.

All of the patient's psychiatric medications except risperidone were re-introduced without a recurrence of toxicity five days prior to discharge. The patient remains well over six months after discharge.

Discussion

When a patient on multiple drugs (as in this case) suffers an adverse effect, it can be extremely difficult to ascribe causality to one of the drugs, particularly when all of the drugs may at some point have been reported to cause the same adverse effect. Particular importance should be placed on the temporal relationship between the start of drug and onset of the reaction, the response to drug withdrawal, and the effect of rechallenge, if this is carried out. Given that only risperidone had been started recently and the patient's signs resolved on its withdrawal, we suspected that risperidone was responsible for the photosensitivity reaction. Furthermore, all the drugs apart from risperidone were re-introduced without recurrence of toxicity. Monochromator testing was consistent with drug-induced photosensitivity; rechallenge with risperidone would have clinched the diagnosis, but this was felt to be ethically unacceptable given the severity of the original reaction and the inability of the patient to give informed consent. There has been only one previous report of photosensitivity to risperidone on the MCA/CSM database in a male

Table 1 Phototesting results. The erythematous thresholds are the lowest doses of light at which erythema is clearly visible

Wavelength ± bandwidth (nm)	24-h minimal erythematous dose (J/cm ²)	
	Normal range	Observed
300 ± 5	>0.14	0.28
320 ± 10	>1	2
330 ± 10	>3.5	14
350 ± 20	>14	10
370 ± 20	>20	14
400 ± 20	>28	113

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Some of the drugs associated with systemic photosensitivity reactions

Antimicrobials

- ciprofloxacin
- griseofulvin
- quinine
- sulphonamides
- tetracycline

Nonsteroidal anti-inflammatory drugs

- azapropazone
- piroxicam
- tiaprofenic acid

Cardiovascular drugs

- amiodarone
- thiazide diuretics

Psychotropic agents

- chlorpromazine
- thioridazine
- protriptyline
- imipramine

Box 1

patient who developed an itchy exfoliating eruption confined to sun-exposed areas nine days after starting risperidone (3 mg bid). The patient recovered following drug withdrawal. There have been no reports of risperidone photosensitivity in the literature. There have also been 24 reports of other types of cutaneous reactions to risperidone on the MCA/CSM database (mostly maculopapular eruptions but also one case each of erythroderma and erythema multiforme). On admission, the patient was also hypotensive, had renal impairment and was in atrial flutter. These were probably a consequence of the photosensitivity and secondary bacterial infection of the skin, although it is important to note that there has been one report each of renal impairment, hypotension and supraventricular arrhythmia with risperidone on the MCA/CSM database.

Risperidone is a new antipsychotic drug with affinity for serotonergic 5-HT₂, adrenergic α_1 and dopaminergic D₂ receptors. Antipsychotic effects at least comparable to haloperidol¹ have been demonstrated, the potential advantage of risperidone being that it also affects the negative symptoms of schizophrenia,² and is less likely to cause extrapyramidal side-effects.³ Clinical trial data suggest that risperidone has a favourable side-effect profile, the most common adverse effects being sedation and weight gain.³ However, clinical experience is limited,

Learning points

- all adverse reactions to new drugs (marked by a ▼) should be reported on yellow cards
- risperidone like other antipsychotics may have the potential to cause photosensitivity, although the risk is unlikely to be as high as with chlorpromazine
- photosensitivity can occur with a wide variety of drugs and in general, is due to either phototoxic or photo-allergic mechanisms

Box 2

and as with any new drug, risperidone is currently under intensive monitoring in the UK (indicated by ▼ in the *British National Formulary*). This means that all suspected adverse reactions to risperidone (serious and non-serious) should be reported to the drug regulatory agencies.

Systemic photosensitivity reactions have been reported with about 50 drugs (box 1).⁴ Of the antipsychotics, chlorpromazine has been the most widely studied, and is liable to induce photosensitivity reactions in 16 to 25% of those treated.^{5,6} In general, photosensitivity can be divided into phototoxic and photo-allergic reactions. Mechanistically, they are differentiated by the fact that the latter is immune-mediated, the antigen being a photoproduct which acts as a hapten, while the former is due to direct toxicity of the drug. The late occurrence of the reaction and spread of the rash beyond the sun-exposed areas is consistent with the reaction in this patient being a photo-allergic reaction. However, this cannot be stated with certainty since there is controversy regarding the criteria for differentiating phototoxic and photo-allergic reactions. Furthermore, sensitivity at different wavelengths cannot be used to distinguish between phototoxicity and photo-allergy since both are usually caused by UVA, although phototoxicity can occasionally be caused by UVB or visible light.

Causality cannot be proved on the basis of this report alone. Risperidone may have the potential to cause photosensitivity, but given its widespread use, the risk is likely to be small, and certainly much less than that seen with aliphatic phenothiazines such as chlorpromazine.

Keywords: risperidone; photosensitivity; adverse drug reaction

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