Adverse Effects of Antituberculosis Drugs

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Summary

Antituberculosis chemotherapeutic regimens do not often cause serious toxicity. When reactions do occur, they must be correctly and rapidly managed so that effective treatment is not unnecessarily interrupted or the patient exposed to the risk of acquired resistance. All the drugs can cause hypersensitivity reactions, particularly streptomycin, thiacetazone and para-aminosalicylic acid, but alternative drugs are readily available. However, if it is necessary to desensitise the patient, this can usually be achieved. Transient symptomless increases in serum liver enzyme concentrations are common during the early weeks of antituberculosis treatment, but these are not clinically important and must be distinguished from clinically evident hepatitis which may occur in up to approximately 1% of patients. When hepatitis occurs, treatment should be interrupted until liver function tests are again normal. Treatment, even with the same drugs, can then usually be resumed uneventfully.

Other reactions are rarely a problem with the dosage schedules now recommended. Isoniazid can cause neurological toxicity, but this can be both prevented and treated by administration of pyridoxine. Rifampicin, whether administered daily or intermittently, may cause gastrointestinal reactions and, rarely, thrombocytopenic purpura. When administered intermittently, or when taken irregularly by the patient, it may cause febrile reactions (the 'flu' syndrome), and, rarely, shortness of breath, shock, acute haemolytic anaemia and acute renal failure. When one of these rare, potentially serious reactions occurs, the drug must be withdrawn immediately and permanently; recovery is then usually complete. Pyrazinamide can cause arthralgia, especially when given daily, but this can be treated symptomatically. Streptomycin and other aminoglycosides are ototoxic and can cause renal damage, but should never cause permanent damage if the drug is withdrawn as soon as there is evidence of serious toxicity. Ethambutol can cause a dose-related retrobulbar neuritis, and must be withdrawn immediately if visual symptoms occur. Para-aminosalicylic acid can cause troublesome gastrointestinal toxicity, and is now rarely used because of this. Thiacetazone can cause renal failure, erythema multiforme, gastrointestinal intolerance, cerebral oedema and haemolytic anaemia, but is nevertheless well tolerated in some communities. Ethionamide and prothionamide may produce troublesome gastrointestinal toxicity, and cycloserine can cause dose-related neurological and psychiatric disturbances.
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All antituberculosis drug regimens can cause adverse reactions. These are usually minor, but occasionally they can be serious and, rarely, even life-threatening. It is necessary for the clinician to be aware of the reactions which may occur, to know how to manage them, and to preserve a balance between the risks to the patient of adverse drug reactions and of so interrupting or modifying treatment as to leave active tuberculosis inadequately treated.

All the main antituberculosis drugs can cause or contribute to cutaneous and generalised hypersensitivity reactions and hepatitis, and these reactions are considered first in this review. The other main reactions which can occur are discussed individually for each drug.

1. Generalised Reactions to Antituberculosis Drugs

1.1 Cutaneous and Generalised Hypersensitivity Reactions

The drugs which most commonly cause cutaneous and generalised hypersensitivity reactions are streptomycin, para-aminosalicylic acid and its salts, and thiacetazone. Reactions to regimens which do not include one or more of these drugs are uncommon and are usually mild and transient.

1.1.1 Clinical Manifestations

The clinical manifestations of hypersensitivity are diverse (Hardie and Savin, 1979), but the most common features are rash and fever (British Medical Research Council, 1973; Medical Research Council Tuberculosis Chemotherapy Trials Committee, 1962). The rash is usually erythematous and itchy, and may be macular or papular; it tends to involve the trunk more than the extremities. Generalised reactions may also include periorbital swelling, conjunctivitis, and systemic symptoms and signs such as rigors, malaise, vomiting, aching limbs, headache, generalised lymphadenopathy, albuminuria, hepatosplenomegaly and occasionally transient jaundice.

Rarely, severe and even fatal exfoliative dermatitis with involvement of the mucous membranes (Stevens-Johnson syndrome) may occur, particularly as a reaction to thiacetazone (East African/British Medical Research Councils, 1966; Miller et al., 1970; Tuberculosis Chemotherapy Centre, 1966), or if administration of a drug is continued once hypersensitivity has developed. Anaphylactic shock may rarely occur if a large dose of a drug is given in error after a previous hypersensitivity reaction.

Hypersensitivity reactions usually occur early in the course of treatment, often within the first 4 weeks; a severe reaction may occur after a single dose if the patient is already hypersensitive to the drug concerned.

1.1.2 Management

Minor reactions which do not distress the patient may be self-limiting and require only symptomatic treatment, for example with an antihistamine, without interrupting or altering the regimen (Ferguson et al., 1971). However, if a reaction other than a trivial one occurs or is suspected, all drug treatment should be stopped until the reaction has subsided. If this is not done, a serious reaction may ensue, and the principles of management are then:

1) Identify the drug or drugs responsible for the reaction.
2) Resume adequate chemotherapy as soon as possible, using not less than 2 drugs to which the patient is not hypersensitive.

The patient should be desensitised to the drug or drugs responsible for the reaction only if this is necessary for the resumption of adequate chemotherapy. Once the reaction has subsided, daily challenge doses to the drugs of the prescribed regimen should be started, the aim being to challenge the patient first to drugs which are least likely to have caused the reaction, so that administration of these can be resumed with the minimum of delay while (if necessary) challenge doses and desensitising doses of other drugs are administered. Challenge doses of each drug of the regimen should be given in the sequence in which they are shown in table I, until a reaction oc-