demonstrates that the cost-minimisation approach used in the studies cited above may not be appropriate for all indications. In addition, the available pharmacoeconomic data do not address the relative merits of parenteral ceftriaxone and oral therapy with broad-spectrum antibacterials (e.g. quinolones, oral third-generation cephalosporins). Oral agents may be suitable for the treatment of serious bacterial infections as either initial therapy or following parenteral therapy.[20,21] Indications for oral therapy may include typhoid fever, and infections involving the respiratory tract, urinary tract, skin, soft tissues and bones, each of which may also be indications for ceftriaxone.[20-23]

Oral therapy offers greater opportunities for cost avoidance than parenteral therapy because:
- acquisition and administration costs may be lower
- the risks of parenteral administration (e.g. phlebitis) are avoided
- early discharge is facilitated because of the ease of self-administration.[21]

References

Ademetionine has clinical potential in depression

Ademetionine† (S-adenosyl-L-methionine) represents a novel approach for the treatment of depression. It is the active derivative of methionine and occurs naturally in the body, acting as a methyl donor. If its rapid onset of action, good tolerability and oral efficacy are confirmed in further trials, ademetionine will be a useful addition to the agents currently available for treating patients with depressive disorders.

Ademetionine has produced clinical improvement in the treatment of intrahepatic cholestasis due to liver diseases or pregnancy.[1,12] It has also shown some efficacy in the treatment of rheumatic disease.[31] However, this review will focus on its potential use in patients with neuropsychiatric disorders.

Role in transmethylation

Endogenous ademetionine is involved in the methylation of a number of molecules including hormones, neurotransmitters and nucleic acids.[1] In the CNS, the formation of ademetionine is dependent on folate and vitamin B12, and is carefully regulated.[4]

Deficiencies in folate and/or vitamin B12 have been found to result in decreased CNS ademetionine levels.[4] Moreover, folate and vitamin B12 deficiencies may result in neurological and psychiatric disturbances.[4]

Low cerebrospinal ademetionine levels have been documented in patients with a number of neurological and psychiatric disorders including depression, Parkinson’s disease, Alzheimer’s dementia and subacute combined degeneration of the spinal cord.[4] In Parkinson’s disease, this may be related to drug therapy with levodopa.[4]

Treatment of neuropsychiatric disorders

The major limitation of ademetionine therapy in earlier trials was that it was only available as a parenteral formulation for intravenous or intramuscular administration. An oral formulation has been evaluated in more recent trials.

Trials in patients with neuropsychiatric disorders have generally used fixed ademetionine dosages, and thus the optimum oral and parenteral dosages have yet to be determined.

† Ademetionine is not available in Denmark, France, Sweden, the Netherlands or the UK; it has investigational status in Canada, and in Germany and Spain it is not licensed for the treatment of depression.
Depression

The efficacy of ademetionine in patients with depression has been studied in a number of small double-blind comparisons with placebo or with selected tricyclic antidepressants.[1,5] In addition, a number of trials have combined both the parenteral and oral routes of administration.

A recent meta-analysis of several of these studies showed that the antidepressant efficacy of ademetionine was superior to that of placebo and comparable to that of tricyclic antidepressants.[5] Prospective studies (n = 13) were included if participants were depressed according to DSM-III criteria and if efficacy became apparent.[6] However, 2 weeks may not be long enough for the effect of tricyclic antidepressants to become apparent.[6]

Patients were considered full responders to treatment if HAM-D scores decreased by ≥50%. By this criterion, the overall efficacy of ademetionine was 38% and that of placebo was 22%. In comparisons with tricyclic antidepressants, 61% of patients responded to ademetionine and 59% to intravenous amitriptyline 100 mg/day or clomipramine (clorimipramine) 100 mg/day, or oral imipramine 140 or 150 mg/day.[5]

In one 6-week study, ademetionine 1600 mg/day showed a more rapid onset of effect than imipramine 140 mg/day, both administered orally.[7] In another study, adjunctive treatment with ademetionine 200 mg/day intramuscularly for the first 2 weeks of oral imipramine therapy was associated with more rapid antidepressant response than adjunctive placebo.[8]

Depression occurs commonly in patients with Parkinson’s disease and may be a result of levodopa therapy, which appears to lower brain ademetionine levels.[4] In one crossover study, ademetionine 800 mg/day orally plus 200 mg/day intramuscularly for 30 days significantly improved HAM-D scores compared with placebo in depressed patients with Parkinson’s disease.[9] Ademetionine did not alter measures of Parkinson’s disease severity or levodopa dosage requirements.

Other conditions

Experience of the use of ademetionine in various other neuropsychiatric disorders is generally limited to very small studies and case reports.[4] Thus, its precise role in these conditions remains to be determined.

In 7 patients with Alzheimer’s dementia, ademetionine 1200 mg/day administered orally for 3 to 5 months improved measures of cognitive function, mood and speed of mental processing.[4]

Folate deficiency may be associated with mood disorders in patients with epilepsy. Moreover, folic acid administration in these patients may impair seizure control.[4] In 7 patients with epilepsy, intravenous ademetionine 200 mg/day had positive effects on mood without altering seizure frequency.[4]

Tolerability

Several reports have suggested that because ademetionine is a ubiquitous metabolite, it is likely to have few adverse effects,[4,5] however, this does not necessarily follow. The accurate tolerability profile of this agent remains to be determined.

In 1 report of the use of ademetionine in 20 641 patients with osteoarthritis, 21% of patients reported at least one adverse event and the withdrawal rate due to adverse events was 5.2%.[11] Most adverse events were gastrointestinal.

In the small numbers of patients treated for depression, reported adverse events include a feeling of elation, headache, insomnia, injection site pain, nausea and vomiting and heartburn.[7-9] A number of patients with bipolar depression have experienced a switch from depression to hypomania.[11]

Serotonin syndrome (the symptoms of which include hyperthermia, hypertension, myoclonus and tremors) occurred in a patient with major affective disorder receiving ademetionine 100 mg/day intramuscularly and clomipramine 75 mg/day.[10] The authors suggested that this could be due to a synergistic action of the 2 drugs.

References