Psychiatric Bulletin (1993), **17**, 223–224

Expert opinion

L-tryptophan and depressive illness: a valuable adjunct to therapy?

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L-tryptophan is an essential amino acid in human nutrition. The minimum daily requirement for adults is in the range of 175 to 250 mg daily and this is normally exceeded in the average western diet which contains 600 to 1000 mg. Excess tryptophan is normally metabolised through the kynurenine pathway and only 1–2% of tryptophan in the diet is converted to 5-HT. The concept that 5-HT had a part to play in depressive illness evolved after the original observation by Ashcroft & Sharman in 1960 that patients with severe depressive illness had lower levels of the metabolite of 5-HT in cerebrospinal fluid compared with controls. In addition, early papers on the therapeutic efficacy of tryptophan suggested that it was potentially as successful as ECT.

Administration of L-tryptophan led to an increase in the synthesis of 5-HT in brain in animals and in csf in man. As a consequence the use of L-tryptophan as a therapeutic agent was on a sound theoretical basis.

Assessment of therapeutic efficacy

There are many papers on the use of L-tryptophan in depressive illness, most however, were performed at a time when double-blind randomised protocols were not 'de rigueur'. Three papers however, conform to current standards of clinical trial design, those of Thompson *et al*, 1982; Bennie *et al*, 1982 and Jaffe & Grimshaw, 1985. The total number of patients examined was 321 and the conclusion was that the efficacy of tryptophan is greater than placebo and equal to some antidepressants. In the trial of Thompson *et al* the efficacy of tryptophan was equal to that of amitriptyline was greater than either alone. Bennie estimated the efficacy of tryptophan to be equivalent to that of mianserin. Of the other negative trials there is a suggestion that the dose of the amino acid may be important. Chouinard *et al*, 1979, found, from a study of the literature, that in unipolar patients, above 6 gms of L-tryptophan is usually ineffective.

It is, however, in the area of severe depression that L-tryptophan as an adjunct to other antidepressant drugs is probably of optimal use. The early studies of Coppen and Pare looked at the combination with a monoamine oxidase inhibitor, tranylcypromine. Subsequent open studies suggest the combination of L-tryptophan, lithium and phenelzine (Barker *et al*, 1987) or L-tryptophan, lithium and clomipramine (Hale *et al*, 1987) in severe depressive illness, that is patients who have failed to respond to other adequate treatments including ECT over a minimum period of two years.

Tryptophan withdrawal

The efficacy of L-tryptophan has recently been highlighted by its withdrawal following concern over the eosinophilia myalgia syndrome (EMS). It was reported by Ferrier *et al* (1990) that of 13 patients on combinations of antidepressant drugs including L-tryptophan 12 relapsed on withdrawal. Relapse occurred rapidly mostly within the first week. These relapses varied in severity, but required readmission to hospital in five of the 13 cases. Re-institution of the drug led to full recovery at 12 months in only four patients with a further partial recovery in four. The implication is that precipitation of a depressive illness by a withdrawal of a drug destabilises the mood such that its re-institution may not necessarily lead to recovery.

Some insight into this rapid relapse was provided by Delgado *et al* (1990); they treated patients who had recovered from depressive illness with a regime which depleted L-tryptophan. Patients relapsed extremely rapidly, within hours, when an amino acid mixture deficient in L-tryptophan was given, but contained other amino acids competing with L-tryptophan for uptake into brain. Of those in their study 14 out of 21 patients relapsed but recovered on reintroduction of L-tryptophan. The symptoms of their illness were recreated in a quite intriguing way. For example, an elderly widow whose depressive illness, from which she had recovered included guilty ruminations surrounding the death of her husband, recapitulated these exactly during the time of her induced relapse. In a similar tryptophan depletion experiment, Young *et al* (1985) showed an increase in

depression in control subjects, and subsequently demonstrated a decrease in sleep latency of some 50%. This particular experiment demonstrated depletion effects on a measurable physiological variable.

The eosinophilia-myalgia syndrome

The eosinophilia-myalgia syndrome consists of the acute onset of muscle pain, arthralgia, fatigue, cough and dyspnoea, together with induration of the skin of the trunk and extremities and can progress to a chronically disabling disorder which includes pulmonary, cardiac and central nervous system changes. It is accompanied by a high peripheral eosinophil count.

In 1990 Hertzman *et al* described the first three patients suffering from this condition, all of whom were taking L-tryptophan. The occurrence of this illness reached almost epidemic proportions and by July 1990 1531 cases had been reported and there had been 27 deaths. The outbreak was not limited to the United States, and a further 171 cases were reported in Europe. Brilliant epidemiological studies linked the emergence of this syndrome to the ingestion of L-tryptophan. More importantly the association was found to be with L-tryptophan from a specific Japanese company. Further analytical investigations associated the syndrome with a contamination peak seen on HPLC peak E. Further research has implicated a new contaminant 3-phenyl-amino-L-aniline (Swinbanks & Anderson, 1992), a contaminant similar to that found in the outbreak of EMS in Spain in 1981 due to contaminated cooking oil, the "toxic oil syndrome". EMS has not been clearly associated with other L-tryptophan manufacturers' products.

As a result of epidemiological evidence linking L-tryptophan with the disorder, the drug was withdrawn in most countries including the UK. However, in Canada, L-tryptophan remains normally prescribable.

Conclusions

L-tryptophan is the amino acid precursor of 5-HT a transmitter which continues to be a strong candidate for the central role in the control of mood. There is evidence for its therapeutic efficacy given alone, but its primary place may well be as part of drug "cocktails" with which to treat severe and prolonged depressive illness, otherwise unresponsive to adequate antidepressant regimes. The reason for its withdrawal appears to be a particular toxic product of a specific manufacturer of L-tryptophan. Its complete withdrawal from the market would deplete the therapeutic armamentarium available to psychiatrists and expose patients already continuing to take the L-tryptophan combined with other medication to a catastrophic destabilisation of their mood state. It is not without relevance that currently some 752 patients in 157 hospitals continue to be prescribed the drug on a "named patient" basis, primarily for resistant chronic severe depression. It is hoped that with appropriate precautions the Committee of Safety in Medicines will decide on a reintroduction of this drug for normal therapeutic purposes.

References

Ashcroft, G. W. & Sharman, D. F. (1960) 5-Hydroxyindoles in human cerebrospinal fluids. *Nature*, **186**, 1050.

Barker, W., Scott, J. & Eccleston, D. (1987) The Newcastle chronic depression: results of a treatment regime. *International Clinical Psychopharmacology*, **2**, 261.

Bennie, E. (1982) Mianserin hydrochloride and L-tryptophan compared in depressive illness. *British Journal of Clinical and Social Psychiatry*, **1**, 90–91.

Chouinard, G., Young, S. N., Annable, L. & Sourkes, T. L. (1979) Tryptophan-nicotinamide, imipramine and their combination in depression. *Acta Psychiatrica Scandinavica*, **59**, 395–414.

Delgado, P. L., Charney, D. S., Price, L. H. *et al* (1990) Serotonin function and the mechanism of antidepressant action. *Archives of General Psychiatry*, **47**, 411–418.

Ferrier, I. N., Eccleston, D., Moore, B. M. *et al* (1990) Relapse of chronic depressives on withdrawal of L-tryptophan. *Lancet*, **336**, 380–381.

Hale, A., Proctor, A. W. & Bridges, P. K. (1987) Clomipramine, tryptophan and lithium in combination for resistant endogenous depression: seven case studies. *British Journal of Psychiatry*, **143**, 213–217.

Hertzman, P. A., Blevine, W. L., Mayer, J. *et al* (1990) Association of the eosinophilia-myalgia syndrome with the ingestion of tryptophan. *New England Journal of Medicine*, **322**, 869–873.

Jaffe, G. & Grimshaw, J. (1985) A placebo-controlled comparison of L-tryptophan and amitriptyline in the treatment of depressive illness in general practice. *British Journal of Clinical and Social Psychiatry*, **3**, 51–55.

Swinbanks, D. & Anderson, C. (1992) Search for contaminant in EMS outbreak goes slowly. *Nature*, **358**, 96.

Thompson, J., Rankin, H., Ashcroft, G. W. *et al* (1982) The treatment of depression in general practice: A comparison of L-tryptophan, amitriptyline, and a combination of L-tryptophan and amitriptyline with placebo. *Psychological Medicine*, **12**, 741–751.

Young, S. N., Scott, E., Smith, E. *et al* (1985) Tryptophan depletion causes a rapid lowering of mood in normal males. *Psychopharmacology*, **87**, 173–177.

A full list of references is available from Professor Eccleston on request