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Clonidine

An Effective Anti-manic Agent?

Three patients suffering from bipolar affective disorder, manic phase, and who were resistant to conservative treatment were successfully treated with clonidine. This would support the nor-adrenergic hyperactivity theory of mania. The rapidity of action of clonidine and its lack of relatively serious side-effects renders it a potential alternative to conventional anti-manic agents.

According to the catecholamine theory of affective disorder, increased central nor-adrenergic transmission has been implicated in the genesis of mania (Schildkraut, 1978). Clonidine is a long-established anti-hypertensive agent with presynaptic agonistic effect resulting in inhibition of the neural release of nor-adrenaline. Side-effects during treatment such as depression and sedation are well documented and have resulted in suggestions for its use as both a possible anti-manic and anxiolytic agent (Hoehn-Sarie *et al*, 1981; Lloyd, 1985). Increasing reports in recent literature suggest that clonidine is a potential adjunct in the treatment of mania (Giannini *et al*, 1983; Zubenko *et al*, 1984). We report here our experience with clonidine in the treatment of three patients. They presented with mania and with a history of bi-polar affective disorder.

Case reports

A 29-year-old male with a negative family history of affective disorder was first diagnosed as a unipolar depression in 1979. He developed his first manic episode in 1982 and has subsequently had several admissions with both manic and depressive episodes. He was maintained on lithium carbonate 1200 mg per day since June 1983 with serum lithium levels consistently ranging around 0.8 to 0.9 mmol/litre. His mania was treated at varying stages with chlorpromazine, haloperidol and lithium with only transient effect. His depressive episodes since 1982 were always post-mania and of brief duration. His last admission was in September 1982 when he was again noted to be markedly loud and vociferous with pressure of speech, flight of ideas, elation and grandiose delusion. He failed initially to respond to haloperidol in doses of 60 mg per day combined with chlorpromazine in doses of 1200 mg per day and his mood began to cycle rapidly between mania and apathetic depressive state. Because of his minimal response he was treated after one month with lithium carbonate 1600 mg per day (serum level 0.9 to 1.14 mmol/litre) for a period of 8 weeks but his mood continued to cycle rapidly as before. He was then given, in addition to lithium carbonate, clonidine 0.1 mg *b.i.d.* because of reports of its anti-manic effect. At this time his score on the Bech-Rafaelsen (BR) mania rating scale was 29. Clonidine doses were increased to 0.2 mg *b.i.d.* within 2 days. Following the increase in the dose of clonidine his BR mania rating scale score dropped to 7. His blood pressure did not alter. He was maintained on clonidine for 3 weeks and it was then withdrawn gradually over one week. Subsequently he was maintained on lithium carbonate 1200 mg per day. He was discharged and has remained asymptomatic up to the time of this report.

A 60-year-old woman with a long history of manic-depressive illness, depressed type, presented with her first episode of mania in April, 1985. She had one previous admission for the treatment of depression in 1970 and was treated on an out-patient basis for several depressive relapses up to the time of her latest admission. Her Bech-Rafaelsen mania rating scale score was 32. She was commenced on chlorpromazine 400 mg daily and chlopenthixol 40 mg daily with no effect after 1 week. At this stage haloperidol 5 mg orally with an intravenous dose of 10 mg was added on a daily basis. She failed to respond for a further 1 week. Haloperidol and chlopenthixol were discontinued and she was commenced on clonidine 0.2 mg daily. She became much more settled within 48 h and was normothymic 4 days later. Her BR mania rating scale score dropped to 5 and she was subsequently discharged on clonidine 0.2 mg daily with thioridazene 100 mg daily and has remained asymptomatic up to the time of report.

A 38-year-old married male with a negative family history of affective disorder was first diagnosed as psychotic depression in October 1983 and subsequently had several admissions for depression and mania. In February, 1985 he was again admitted with another episode of mania. His Bech-Rafaelsen mania rating scale score was 31 at the time of admission. He was commenced on chlorpromazine 300 mg daily and 100 mg intramuscular every 6 h with no improvement. After 5 days, haloperidol 10 mg intravenous daily was added to the regimen. He failed to respond for a further 4 days. Haloperidol was discontinued and he was commenced on clonidine 0.1 mg *b.i.d.* He became much settled within 3 days. The dose of chlonidine was increased to 0.2 mg *b.i.d.* and chlorpromazine was reduced to 100 mg a day. He became normothymic within 1 week. His BR mania rating scale score dropped to 6 and he was subsequently discharged on a maintenance dose of clonidine 0.2 mg daily and chlorpromazine 100 mg daily. He has also remained asymptomatic up to the time of report.

Discussion

The three case reports suggest that clonidine may have a role in the treatment of mania and are

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consistent with previous reports. (Giannini *et al*, 1983; Zubenko *et al*, 1984). All the three cases responded rapidly following commencement of treatment with clonidine and without apparent sedative effect. It is also worth noting that no patient developed hypotension or depression. The specific anti-manic effect appears to support the noradrenergic hyperactivity theory of mania (Schildkraut, 1978). Reports of relapse into mania following withdrawal of clonidine would also support this theory (Zubenko *et al*, 1984). Furthermore, Farsang & Kunos (1979) observed that clonidine may act as an endorphinergic agent, particularly in view of the fact that its hypotensive effectives are antagonised by naloxone, as a consequence it has been suggested that clonidine may exert its antimanic effect by stimulating central endorphins. It would appear likely that it has a dual endorphinergic and noradrenergic antagonistic mechanism. While it is preemptive to suggest that clonidine should be used as a standard treatment in mania, our study would suggest that it is worth considering in refractory cases or in patients who cannot tolerate lithium. The associated risks of neuroleptics such as anticholinergic effects, extrapyramidal symptoms and the potential risk of tardive dyskinesia are markedly more serious than those attributed to clonidine such as sedation, hypotension and less commonly depression. Our findings are consistent with other preliminary reports and the possibility of clonidine being used in place of neuroleptics and as an adjunct or substitute for lithium warrant further research.

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The Role of Food Substitutes in a Token Economy System

Data from five behaviour management (token economy) units were analysed for periods of 10–20 weeks before and after the use of a food substitute (Complan®), provided when insufficient tokens had been earned to buy a full- or part-meal. The efficacy of this form of negative punishment to control disturbed and aggressive behaviour was examined. No evidence was found to suggest that the contingent use of a food substitute made any contribution to the therapeutic process.

It was demonstrated in the early 1960s that food could function as a powerful reinforcer of desirable behaviours among patients with psychotic disturbances (Ayllon, 1963; Ayllon & Haughton, 1962). Consequently, several early Token Economy Programmes (TEPs) utilised meals as one form of token-contingent reward. The techniques of behaviour modification have been a cause of ethical concern to several authorities (Wexler, 1973, 1975; Stolz, 1976; Kazdin, 1977; Innis, 1981). To support these

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