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METOCLOPRAMIDE IN TARDIVE DYSKINESIA

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SUMMARY

The effect of single intravenous doses of metoclopramide (10 mg, 20 mg and 40 mg) have been compared with placebo (saline) in a double blind randomised study in 10 patients with tardive dyskinesia following long term neuroleptic therapy. Tardive dyskinesia rating scores were decreased significantly ($P<0.01$) 6 hours after administration of metoclopramide 20 mg and 40 mg when compared with placebo. Reduction of tardive dyskinesia by metoclopramide-a D_2 receptor blocking agent suggest that D_2 receptors may be involved in the mediation of this syndrome.

Tardive dyskinesia is an abnormal movement disorder involving predominantly buccolingual masticatory muscles in patients receiving neuroleptic therapy on a long term basis. The movements are diminished if the dose of neuroleptic drug is increased (Kobayashi, 1977), and the disorder may be due to increased dopaminergic activity within the central nervous system, occurring as a result of chronic dopamine receptor blockade (Klawans, 1973).

Drugs of varying groups have been tried in the treatment of tardive dyskinesia (Mackay and Sheppard, 1979) hypothesising various etiological factors (Gardos *et al.*, 1977). There is some evidence from animal studies that D_2 receptors may mediate peri-oral dyskinesias in guinea pigs (Costall and Naylor, 1978). Therefore now a days interest is being focussed on the use of drugs which specifically block D_2 receptor sites e. g. pimozide and the substituted benzamides like oxiperomide, tiapride and metoclopramide (Kebabian and Calne, 1979). Of these drugs only pimozide has been studied in tardive dyskinesia (Claveria *et al.*, 1975). However, in the treatment of L-dopa induced dyskinesia both oxiperomide (Bedard *et al.*, 1978) and tiapride (Lees *et al.*, 1979) have been reported to be of value but metoclopramide (Tarsy *et al.*, 1975) seemed to be ineffective. We have therefore tried to investigate the potential of metoclopramide in the treatment of tardive dyskinesia following long term neuroleptic therapy.

MATERIAL AND METHOD

An informed consent of the patients and next of kin was obtained. Ten patients (seven women and three men) diagnosed as tardive dyskinesia by two psychiatrists independently were taken up for study. All medications were stopped for 1 month prior to study. The patients selected were between the age range of 35 and 50 years.

The study was double blind and the order of drug administration was randomized for each patient. Patients were given, in random order, single intravenous injections of either placebo (saline) or metoclopramide (10 mg, 20 mg or 40 mg) between 9.30 and 10.00 A. M. on the study days. Every patients received all four treatments at an interval of 7 days between treatments. Patients were assessed for dyskinetic movements, using

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TABLE 1. *The NIM dyskinesia score: Each feature is scored from* 0 (*norma'*) *to* 4 (*Maximal abnormality*).

	Score
1. *Facial and Oral Movements*	
Muscles of facial expression	0—4
Lips and peri-oral area	0—4
Jaw	0—4
Tongue	0—4
2. *Exteremity Movements*	
Upper Limbs	0—4
Lower Limbs	0—4
3. *Trunk Movements*	
Neck, shoulder and hips	0—4
4. *Restlessness*	0—4

the first seven items on the NIMH scale (NIMH Psychopharmacology Research Branch, 1975) (Table-1). Abnormal movements were scored on the scale immediately before the injections and at 1, 3 and 6 hours afterwards by two psychiatrists.

The individual scores for the various dyskinetic movements were summed ('sum dyskinesia score') and the results were analysed to find out mean and standard error of mean for each group-and the statistical significance was found out using two tailed student's 't' test.

RESULTS

There was a significant ($p<0.01$) reduction in the sum dyskinesia score at 1, 3 and 6 hours with all treatments except metoclopramide (10 mg) and placebo (Table 2)

TABLE 2. *Sum dyskinesia score before and after treatment with metoclopramide.*

DRUGS	Score (mean±S.E.M.)			
	Before treatment	After treatment@		
		1 h	3 h	6 h
Saline (placebo)	19.6±1.1	18.3±0.9	17.3±1.0	17.2±0.9
Metoclopramide 10 mg	19.5±1.1	18.5±1.1	17.7±1.1	17.5±1.0
Metoclopramide 20 mg	19.1±1.0	15.1±0.9*	11.9±0.6*	11.2±0.7*
Metoclopramide 40 mg	19.4±0.9	13.4±0.7*	10.6±0.6*	8.7±0.5*

@ value was compared with score before treatment

* $p < 0.01$

DISCUSSION

Effective treatment of tardive dyskinesia has not yet been achieved. So far only treatment of tardive dyskinesia has been the omission of neuroleptic drug, though increase in the dose of neuroleptic drug results in temporary cessation of dyskinetic movements (Inoue, 1979).

The present study was designed to assess the potential of metoclopramide in the control of tardive dyskinesia. We have seen that metoclopramide decreases dyskinetic movements after single intravenous injection (20 and 40 mg). Oxiperomide and tiapride—the other representatives of substituted benzamide compounds have been found to be effective in l-dopa induced dyskinesia (Bedard *et al.*, 1978; Lees *et al.*, 1979) and it has been suggested that this antidyskinetic action is mediated through D_2 receptor blockade. We therefore suggest that the antidyskinetic action of metoclopramide is also mediated through blockade of D_2 receptors since it bears structural resemblance to oxiperomide and tiapride.

The maximum clinical antidyskinetic action was observed at 6 hours interval after administration of the drug though C. N. S. effects of metoclopramide occur within 15 minutes of intravenous administration (Batesman *et al.*, 1978). We have no explanation for this delayed antidyskinetic action of metoclopramide which needs further research.

Metoclopramide itself has been reported to produce tardive dyskinesia (Lavy *et al.*, 1978). In this respect it resemble neuroleptic compounds though metoclopramide does not possess neuroleptic action in human beings (Nakra *et al.*, 1975). However, in animals metoclopramide has been shown to have an antipsychotic action when used in combination with tolazoline, propranolol, phenobarbitone, phenytoin or mepyramine (Hemnani and Dashputra, 1982).

Our studies suggest that stimulation of D_2 receptors is, at least in part, responsible for tardive dyskinesia as it is alleviated by metoclopramide which is a selective D_2 receptor blocking agent. The effect of long term metoclopramide therapy on tardive dyskinesia has been undertaken by us to explore whether the danger of breakthrough supersensitivity exist with metoclopramide as with neuroleptic drugs.

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