

Extrapyramidal Symptoms in Children and Adolescents Treated with Different Doses of Low Potency Neuroleptics

M. Hassib El-Defrawi and A. Atef

The authors evaluated neuroleptic-induced extra-pyramidal symptoms (EPS) in 61 children and adolescents over four weeks of treatment. In patients treated with low potency neuroleptics, EPS was twice as common with higher doses >300 mg, (60%) than with lower doses <299, (26%) mg chlorpormazine equivalents. In patients who were neuroleptic-free before initiation of drug treatment, EPS were more than three times as common in higher doses (73%) than in lower doses (18%). The authors discusses the implications of these findings and suggests the use of prophylactic antiparkinsonian agents in combination with higher doses of low potency neuroleptics.

(Egypt.J. Psychiat.,1994, 17:176-182).

Introduction

Neuroleptic-induced extrapyramidal symptoms (EPS) in children and adolescents are similar to those occurring in adults and include: acute dystonic reactions, akathisia, parkinsonian-like signs, and, after longer use, tardive dyskinesia. (TD). While there is no general agreement among clinicians as to the rates of these movement disorders in psychiatrically hospitalized children and adolescents, these rates have been linked to a number of factors (Richardson et al, 1991) including biological vulnerability, neuroleptic potency, (Kane, 1994) dosage (Koreen et al, 1994) and duration of neuroleptic exposure (particularly for TD), age and sex. For example, Chiles (1978) described acute extrapyramidal reactions in 100% of eleven psychotic adolescents aged 13 to 18 being treated with high potency neuroleptics. These acute EPS are dose dependent and usually occur

within the first few days of treatment with neuroleptic agents. Barnes (1992) Keepers et al (1983), in a retrospective study, suggested an incidence of 90% for acute EPSs in younger patients in the 10 through 19 group during the first 21 days of neuroleptic treatment. In that study, examination of individual EPSs revealed that acute dystonic reactions occurred in 64%, parkinsonism in 53%, and akathisia in 17%. The neuroleptics investigated were mainly high potency agents.

According to a survey by Polizos and Engelhardt (1978) in a series of drug trials, EPSs were one of the three most frequent (25%) side effects of neuroleptic treatment-high-potency drug (67%) compared to those treated with low-potency drugs (26%). However, the doses of low potency neuroleptics used were below used below 300 mg chlorpromazine mg equivalents. Other studies suggest similar rates (Kaplan et al, 1994 and Richardson et al, 1991).

Furthermore, prophylaxis with antiparkinson agents (AP) has been demon-

M. Hassib El-Defrawi, Assistant Professor Department of Psychiatry.

A. Atef, Lecturer of Pediatrics, Suez Canal University.

strated to be greatly effective to reduce the occurrence of EPS in the 10 through 19 year old patients (keepers et al 1983). However, drug guidelines as well as clinical wisdom have suggested withholding the use of initial combinations of neuroleptic and AP agent till EPS develops (The American Psychiatric Association, 1984 and Committee on therapeutics, 1983). These precautions stem from a concern about the potential risk of AP agents to induce CNS toxicity (Mengech, 1984), drug abuse (Pullen et al, 1984), and exacerbation of TD (Gardos and Cole, 1983).

This study was carried out to address the incidence of EPS in children and adolescents treated with different doses of low potency neuroleptics.

Subjects and Method

The study design and protocol were approved by hospital. All patients younger than 18 years were examined soon after admission, usually within the first 48 hours. Over a seven-month period (December 1992-July 1993), consecutive unduplicated admissions totaled 99. All patients who required neuroleptic medication, were hospitalized in the facility for at least two weeks, and free from active medical and neurological problems were considered suitable for the study regardless of their diagnoses.

Sixty one patients aged 8 - 18 years were surveyed. Of those who were not included in the study (N = 38), 5 were juvenile offenders, 2 had focal neurological disorders, one received an antidepressant drug, and the remaining 30 patients did not receive neuroleptic treatment and / or were discharged before two weeks.

There were two low-potency and two high-potency neuroleptics used, and neuroleptic dosages were translated into mg chlorpromazine equivalents (Davis, 1975). Serum levels of neuroleptics were monitored after two weeks of treatment.

Diagnoses were according to DSM-III-R and the ward psychiatrist completed the Brief Psychiatric Rating Scale for Children (BPRS-C) (Overall and Pfefferbaum, 1982) on admission. Patients who developed acute EPS during the study received additional evaluation at that. All other assessments were carried out by investigators blind to the patient's clinical information.

Assessment of the extrapyramidal syndromes was done at a baseline on admission, after two and four weeks of neuroleptic treatment. The assessment procedures included a standardized neurological examination for the presence and severity of parkinsonism, akathisia, acute dystonia and tardive dyskinesia. The scales used were: Simpson-Angus Neurological Rating Scale (NRS) (Simpson and Angus 1970) the Simpson Abbreviated Rating Scale (ADS) (Simpson et al, 1979), and the abnormal Involuntary Movements Scale (AIMS) ((Guy, 1976). Each patient was examined by one of the two investigators (M.E.D. & A.A.) who were trained in the use of these instruments. For the purpose of comparison, patients were considered positive for parkinsonism if they score 4 or more on the first ten items of the NRS. The interrater and test-retest reliability coefficients on the global severity score (NRS) were .96 and .86 respectively.

Results

Initial analysis showed that there were no significant differences between those included in the study (N=61) and those who not (N=38) regarding ages, sex, and ethnicity. However those with a diagnosis of conduct disorder, history of neuroleptic treatment, and previous hospitalization were more likely to stay and receive neuroleptic treatment. For the purpose of comparison, patients were divided into two groups according to

Table (1)
Extrapyramidal Symptoms (EPS) Over 4 Weeks
of Treatment with Low - Potency Neuroleptics

Dosage in Chlorpromazine mg equivalents	Group I				Group I			
	0-299 Mg (N=11)		300 Mg (N=11)		0-299 Mg (N=16)		300 Mg (N=15)	
	N	%	N	%	N	%	N	%
Acute Dystonia	0	(0)	2	(18)	0	(0)	2	(13)
Akathisia	0	(0)	1	(9)	1	(6)	0	(0)
Parkinsonian like Symptoms	2	(18)	5	(46)	4	(25)	7	(47)
@ Total	2	(18)	8	(73)	5	(31)	9	(60)

@Low-dose vs. High-dose x No EPS vs. All EPS: Chi-square= 6.8, df=1: $p<0.01$

whether or not they were receiving neuroleptic drugs before the baseline evaluation. Group II, (N=36, 56%), was composed of patients receiving neuroleptic drugs for two weeks or more before the baseline evaluation. There were no significant differences between group I and group II regarding age, sex, ethnicity, diagnosis, full scale I.Q., previous hospitalization, history of EPS, total score of BPRS-C, and neuroleptic dosage in chlorpromazine equivalents. Group II had a significantly longer duration of neuroleptic treatment: mean (SD) 10.1 ± 13.8 for group I vs. 27.4 ± 26.6 months for group II ($F=8.84$, $p<0.01$).

Low-potency neuroleptics (chlorpromazine & thioridazine) were the most commonly used drugs in groups I and II (88% vs. 86%). Neuroleptic doses ranged from 25 to 1500 mg chlorpromazine. Both group I and II were further differentiated according to daily dosage into 0-299 mg and 300+ mg chlorpromazine equivalents subgroups.

When agents of high potency neuroleptics were separated from those of low

potency neuroleptics Table (1), EPSs (in both groups I and II) were twice as common in patients receiving higher doses (N=17, 65%) than those on lower doses (N=7, 26%) ($X^2=6.8$, $df=1$, $p<0.01$).

There were no significant differences between the doses in similar subgroups of patients: mean (SD) 152.3 ± 67.5 and 129.7 ± 69.3 mg chlorpromazine equivalents in the low doses subgroups vs. 544.5 ± 297.9 and 573.3 ± 289 mg chlorpromazine equivalents the high dose subgroups.

In group I, EPSs were more than three times as common in higher doses (N=8, 73%) than in lower doses (N=2, 18%) ($X^2 = 4.58$, $df=1$, $p<0.05$). Nine patients in group II showed evidence of parkinsonism on admission. When they were separated from the total number of patients who developed EPS during neuroleptic treatment, EPS still occur in higher rates in patients on higher doses (N=12, 67%) than in those on lower doses (N=7, 27%) ($X^2=5.2$, $df=1$, $p<0.05$). There was no significant association between serum neuroleptic levels

and EPS.

Acute dystonic reactions occurred in four patients in group II (two were receiving high potency neuroleptics) where their antiparkinson (AP) agent was discontinued after admission. The only patient who developed akathisia in group I has a history of oculogyric crisis and spasm of the tongue. As an outpatient he received I.M. depot neuroleptic plus an AP agent because of noncompliance with medication. After admission, he was treated with 400 mg chlorpromazine and also exhibited parkinsonism.

Discussion

The small number of patients in comparison to the multitude of variables inspected and the naturalistic setting of our survey preclude generalization. However, the findings are provocative in terms of clinical patient care and future research.

Extrapyramidal side effects occurred in both groups I and II, in low-dose and in high-dose subgroups, whether patients were receiving low-potency or high-potency neuroleptics. Twenty six percent of the patients receiving low-doses low-potency neuroleptics (chlorpromazine and thioridazine) developed EPS. This rate (26%) matches the figure (26%) described by Engelhardt and Polizos (1978) in children receiving low-potency neuroleptics in doses below 300 mg chlorpromazine equivalents. (Richardson et al, 1991). However when high-doses of low-potency neuroleptics are considered, higher rates of EPS were found particularly in those patients who were neuroleptic-free before initiation of drug treatment (73%). These findings are important for several reasons. (Kaplan et al, 1994). First, previous reports concerning the low incidence of EPS with low potency neuroleptics usually administer doses below 300 mg chlorpromazine equivalents and did not measure EPS sys-

tematically Engelhardt and Polizos (1978). Second, none of these patients received AP treatment except those patients who developed the acute dystonic reactions. One possible explanation could be that the use of a standardized neurological assessment to detect EPS probably identifies subtle cases that usually go unrecognized. (Reardon et al, 1989). Acute dystonic reaction is easier to identify and treat. On the contrary, signs of parkinsonism are usually slow in onset, may be subtle in nature, and the developing akathisia could be considered as a sign of improvement and response to treatment rather than a side effect.

Third, low-potency neuroleptics have been used extensively in pediatric psychopharmacology and the common experience is that these drugs have a high anticholinergic activity and should be less likely to induce EPS as they exert a possible antiparkinsonian effect. This might be true for acute dystonic reactions, but not for parkinsonian side-effects. When less potent neuroleptic is used at higher dose levels, the resultant amount of dopamine-receptor blockade is equivalent to a more potent compound used in lower doses. This experience is supported by the finding that acute dystonic reactions occurred in 18% and 13% in group I and II, while parkinsonian-side effects occurred in 46% and 47% respectively. However, the magnitude of the present findings suggests that the current practice of withholding AP drugs until the development of EPS may need to be reassessed. This conclusion is supported by the fact that the four patients in group II developed acute dystonic reactions when their AP agents were discontinued after admission. This suggests that a sizable proportion of patients appear to need AP agents to control neuroleptic-induced EPS (Jellineck et al, 1981).

Initial prophylaxis with AP agents appeared to be greatly effective in the 10 through 19-year-old patients (Keepers et al, 1983 and Kaplan et al, 1994)). In addition, the higher incidence of EPS in high dose low-potency neuroleptics when used without AP agents suggests that AP agent could be used when low potency neuroleptics are prescribed in higher doses or that the use of prophylactic AP agents in combination with high-potency neuroleptics might be an alternative choice in view of the sedative nature of low-potency neuroleptics. Low-potency neuroleptics are reputed to affect the learning process and cognitive functions in disadvantaged children (Breuning et al, 1983) and there are controlled studies suggesting the advisability of haloperidol in the treatment of mentally retarded and psychotic children (Levan, 1971 and Serrano, 1973). Akathisia occurred in two patients only (9% and 7%) which is in agreement with other studies (2,3) and may reflect a biological or metabolic difference in children and adolescents. Akathisia is difficult to assess, particularly in disadvantaged children and adolescents where motor restlessness might be seen as hyperactivity and aggressiveness. However, future studies should be directed at investigating rates of EPS in patient groups randomly assigned to low-dose and high-dose low-potency neuroleptics, with standardized dosage and blind EPS ratings.

Only 8 patients received high-potency neuroleptics, six patients received haloperidol, and two patients received trifluoperazine in doses above 300 mg chlorpromazine equivalent per day. Two of these patients developed acute dystonia and were given AP treatment. Five patients received initial prophylaxis with AP agents, only two of whom showed evidence of EPS. One patient who did not receive an AP agent, showed

evidence of severe parkinsonism. Evidence suggests that there is a threshold level for anticholinergics above which EPS are unlikely to occur in patients receiving neuroleptics (Tune and Cole, 1981). However the sample is too small to draw any definitive conclusions. Prospective investigations are suggested to determine the prophylactic effectiveness of AP agents with high dose low-potency neuroleptics in which patients are randomly assigned to AP drugs or placebo with patients blindly assessed for EPS.

References

- Barnes, T.R.E. (1992) Neuromuscular effects of neuroleptics: akathisia. In *Adverse Effects of Psychotropic Drugs* (eds. J. M. Kane & J. A. Lieberman). New York: Guilford Press.
- Breuning, S.E., Ferguson, D.G., Davidson, N.A. (1983) Effects of thioridazine on the intellectual performance of mentally Retarded drug responders and nonresponders. *Arch. Gen. Psychiat.*, 40: 309 - 3113.
- Chiles, JA. (1978) Extrapyramidal reactions in adolescents treated with high-potency antipsychotics. *Am. J. Psychiat.*, 135: 239-240.
- Committee on Therapeutics (1983) *Psychopharmacotherapy for institutionalized children and adolescents*. New York State Office of Mental Health, Albany, New York.
- Davis, J.M. and Cole, J.O. (1975) Antipsychotic drugs in *Comprehensive Textbook of Psychiatry*, 2nd ed., vol 2. Edited by Freedman AM, Kaplan HI, Sackoff BJ. Baltimore Williams & Wilkins Co.
- Engelhardt, D.M. and Polizos, P. (1978) Adverse effects of pharmacotherapy in childhood psychosis. Edited by Lipton

- M.A., DiMascio, A. and Killam, K.F. New York, Raven Press.
- Gardos, G. and Cole, J.O. (1983) Tardive dyskinesia and anticholinergic drugs. *Am. J. Psychiat.*, **140**: 200 - 202.
- Guy, W. (1976) ECDEU Assessment Manual for Psychopharmacology. Rockville Md, NIMH Psychopharmacology Research Branch.
- Jellinek, T., Gardos, G. Cole, J. (1981) Adverse effects of antiparkinson drug withdrawal. *Am. J. Psychiat.*, **138**: 1567-1571.
- Kane, J.M. (1994) The use of higher dose antipsychotic medication (Editorial) *Brit. J. Psychiat.*, **164**: 431-432.
- Kaplan, S.L., Simms, R.M. and Busner, J. (1994) Prescribing practices of outpatient child psychiatrists. *Amer. J. Acad. Child Adolesc. Psychiat.*, **33**: 35-44.
- Keepers, G.A., Clappison, VJ., Casey, DE. (1983) Initial anticholinergic prophylaxis for neuroleptic-induced extrapyramidal syndromes. *Arch. Gen. Psychiat.*, **40**: 1113 - 1117.
- Koreen, A.R., Lieberman, J., Alvir, J., Chakos, M., Loebel, A., Cooper, T. and Kane, J. (1994) Relation of plasma fluphenazine levels to treatment response and extrapyramidal side effects in first - episode schizophrenic patients. *Amer. J. Psychiat.*, **151**: 35-39.
- Levan, L.J. (1971) Clinical comparison of haloperidol with chlorpromazine in mentally retarded children. *Am J Ment Deficiency* **75**: 719 - 723.
- Mengech, H.N.K.A. (1984) Psychiatric Manifestation of benzhexol toxicity. *East Afr Med. J.* **61**: 78 - 81.
- Overall, J.E. and Pfefferbaum, B. (1982) The Brief Psychiatric Rating Scale for Children. *Psychopharmacol. Bull.* **18**: 10 - 16.
- Pullen, G.P., Best, N.R. and Maguire, J. (1984) Anticholinergic drug abuse: a common problem? *Br. Med. J.* **289**: 612 - 613.
- Reardon, G.T., Rifkin, A. and Schwarz, A. (1989) Changing pattern of neuroleptic dosage over a decade. *Amer. J. Psychiat.*, **146**: 726-729.
- Richardson, M.A., Haugland, G., Craig, T.J. (1991) Neuroleptic use, parkinson an symptoms, tardive dyskinesia and associated factors in child and adolescent psychiatric patients. *Amer. J. Psychiat.*, **148**: 1322-1328.
- Serrano, AC. Forbis, O.L. (1973) Haloperidol for psychiatric disorder in children. *Dis. Nerv. Syst.* **34**: 226-231.
- Simpson, G.M. Angus, J.W.S. (1970) A Rating Scale for extrapyramidal effects. *Acta Psychiatr Scand, (supplement)* **212**: 11 - 19.
- Simpson, G.M., Lee, J.M., Zoubok, B. (1979) A Rating Scale for tardive dyskinesia. *Psychopharmacology (Berlin)* **64**: 171 - 179.
- The American Psychiatric Association Commission on Psychiatric Therapies (1984) Antipsychotic Agents, in Part I Somatic Therapies. Washington DC, American Psychiatric Association.
- Tune, L. and Cole, J.T. (1981) Acute extrapyramidal side affects: serum levels of neuroleptics and anticholinergics. *Psychopharmacology* **75**: 9 - 15.

Les Symptomes Extrapyramidals Chez les Enfants et les adolescents Traités avec des doses differentes des neuroleptics moins puissants

L'auteur a évalué les symptomes extrapyramidals induit par les neuroleptics chez 122 enfants et adolescents durant 4 semaines du traitement. Les resultats ont démontré que le pourcentage de ces symptomes (EPS) chez les patients traités avec les neuroleptics moins puissants est relativement haut avec les plus grande doses. Finalement l'auteur discute les implications de ces conclusions.

الأعراض خارج الهرمية في الأطفال والمراهقين الذين يعالجون

بجرعات مختلفة من المهدئات العظمى منخفضة الفعالية

تم في هذا البحث تقويم أعراض الجهاز خارج الهرمي في ٦١ طفلاً ومراهقاً من الذين يعالجون بالمهدئات العظمى من النوع منخفض الفعالية ولدة أربعة أسابيع، وذلك باستخدام مقاييس عصبية مقننة للفحص والتقويم العصبي. وقد أظهرت النتائج أن أعراض الجهاز خارج الهرمي قد حدثت وانتشرت بدرجة مضاعفة وذات دلالة إحصائية في الأطفال والمراهقين الذين يعالجون بجرعات من المهدئات العظمى ذات الفعالية المنخفضة أكثر من ٢٠٠ مجم مكافئ للكلوربرومازين بالمقارنة بهؤلاء الأطفال الذين تناولوا جرعات أقل من ٢٠٠ مجم مكافئ للكلوربرومازين.

وقد ظهرت الأعراض خارج الهرمية مع الجرعات الكبيرة من المهدئات العظمى منخفضة الفعالية في هؤلاء الأطفال والمراهقين الذين كانوا لا يتعاطون هذه المهدئات بثلاثة أضعاف (٧٣٪) عن هؤلاء الذين كانوا يتناولونها بانتظام من قبل (١٨٪) ويناقش البحث دلالات النتائج في ضوء ممارسة وصف المهدئات العظمى منخفضة الفعالية وضرورة إعطاء مضادات الشلل الرعاش في بداية العلاج.