

EFFICACY OF ACTH 4-9 ANALOG, METHYLPHENIDATE, AND PLACEBO ON ATTENTION DEFICIT DISORDER WITH HYPERKINESIS

HENDRIK J. BUTTER,^{1,4} YVON LAPIERRE,^{1,2,5}
PHILIP FIRESTONE,³ and ARTHUR BLANK,³

Departments of ¹ Psychiatry, ² Pharmacology, and ³ Psychology,
University of Ottawa, Ottawa, Ontario; ⁴ Centre hospitalier
Pierre-Janet, Hull, Quebec; and ⁵ Royal Ottawa Hospital,
Ottawa, Ontario, Canada.

(Final form, July 1984)

Abstract

Butter, Hendrik J., Yvon Lapierre, Philip Firestone and Arthur Blank: Efficacy of ACTH 4-9 analog, methylphenidate and placebo on attention deficit disorder with hyperkinesis. Prog. Neuro-Psychopharmacol. & Biol. Psychiat. 1984, 8 (4-6): 661-664.

1. The present study compared the efficacy of ACTH 4-9 analog, methylphenidate, and placebo on attention deficit disorder with 30 (HK) children with attention deficit disorder and psychometric measurements.
2. HK children were randomly placed into three groups, according to body weight, and treated with placebo, methylphenidate, and adrenocorticotrophic hormone fractions (ACTH 4-9 analog).
3. The results revealed that HK children on methylphenidate manifested a significantly greater vasomotor reactivity, behavioral improvement, and learning receptivity than HK children taking ACTH 4-9 analog and/or placebo.
4. Future research implications with ACTH 4-9 and HK children are discussed.

Keywords: ACTH 4-9 analog, Methylphenidate, Attention Deficit Disorder

Abbreviations: Adrenocorticotrophic hormone (ACTH); Hyperkinesis (HK); Conners's Short Form Rating Scale (CSS); Matching Familiar Figure Test (MFF); Memory for Design (MFD).

Introduction

It is becoming increasingly apparent that short-chain polypeptides such as melanocyte stimulating hormone and analogues adrenocorticotrophic hormone (ACTH) fractions (ACTH 4-9) influence both behavior and the electrophysiological activity of the brain.¹ More precisely, ACTH 4-9 analog studies¹⁻⁴ have reported enhancement of short-term visual memory, attention, self-rated competence, and observer-rated sociability. These behavioral and neurophysiological findings indicated that ACTH and its fractional analogues have direct, extra-adrenal effects on central nervous system functioning.

Attention deficit disorder with hyperkinesis (HK) is now quite well recognised as a clinical syndrome in children who manifest difficulties in attention, memory, and motivation, with or without hyperactivity.⁵

Studies⁶⁻⁸ investigating the management of the disorder have reported that methylphenidate reduces distractibility and impulsivity and improves selective attention in both home and school environments. Consequently, methylphenidate has become the usual chemotherapeutic strategy for children with this syndrome.

The objective of the present investigation was to: compare ACTH 4-9 with placebo to determine whether or not the peptide improves measurements of attention and behavior in hyperkinesis children.

Methods

Patient Population. Thirty children were included in the study. They were all male, aged 6 to 12 years, and had a clinical diagnosis of attention deficit disorder with hyperkinesis (DSM 111).

Drug Administration. This was a double-blind efficacy study comparing three groups of 10 boys, each group receiving a different drug over a 1-week period. Dosage was adjusted for body weight as illustrated in Table 1.

Table 1

Parameter Taken to Study the Effects of ACTH 4-9 Analog, Methylphenidate

	Weight groups		
	A	B	C
Weight ranges (kg)	16-25	26-35	36-45
No. of subjects	10	13	7
Fixed doses of drug (mg)	10	15	20
Dose ranges (mg/kg)	0.62-0.40	0.57-0.43	0.56-0.44

Experimental Procedure. Seven-day drug-free period was followed by a week of placebo treatment. After the placebo washout, treatment was assigned in a double-blind and random manner to either ACTH 4-9, methylphenidate, or placebo.

Assessment Instruments. Clinical and laboratory instruments: Summary description of ACTH 4-9 dependent variables as illustrated in Table 2.

Statistical Analysis. Table 2 illustrates the type and procedure of quantification used for each index in the current study. In order to explore the pre-residual and post-residual drug change, the BMPD-P2V program was used.⁹

Results

The results revealed that the three treatment groups on each of the dependent variables, only the digital blood flow measured at the end of the experimental session and the Conners' HK index were significantly different on the predrug and postdrug comparisons. HK children treated with methylphenidate had a significant lower digital blood flow and hyperactivity index after 1 week of drug administration than HK children on placebo and ACTH 4-9 analog.

Electroencephalogram, hematology, blood chemistry, and urinalysis were within normal limits prior to treatment and remained so after treatment for all three weight and drug groups.

Discussion

The primary purpose of the present investigation was to compare three groups of HK children on placebo, methylphenidate, and ACTH 4-9 in a randomized group design.

Despite the limitations of the sample size, short time exposure, and difficulties of available psychometric instruments, these results suggest that methylphenidate produces a significantly higher pulse rate and lower skin conductance in comparison to ACTH 4-9 and/or placebo. This is consistent with earlier reported findings on methylphenidate efficacy.¹⁰

Table 2
List of ACTH 4-9 Dependent Variables

System	Index	Quantification
Psychometric	Memory for design	msec
	Matching familiar figures:	
	Latency	sec
	Errors	errors
	Reaction time	msec
	Mean reaction time	msec
Clinical	Conners' rating	0-30 points
	Conners' teacher	0-50 points
Psychophysiology	Digital pulse volume (DPV) (individual range corrections):	Mean number of mm over a period of every 10 sec during 10-min relaxation
	$\emptyset_{ix} = \frac{DPV_{ix} - DPV_i(\min)}{DPV_i(\max) - SE_i(\min)}$	
	Skin conductance (SC)(individual range corrections):	Mean SC level in mho every 10-min relaxation
	$\emptyset = \frac{SC_{ix} - SC_i(\min)}{SC_i(\max) - SC_i(\min)}$	

However, an interesting observation made by parents of three HK children on ACTH 4-9 was that their children were more sociable while on the peptide. That observation was supported by a reduction in the Conners' HK index as rated by the teacher. The improvement in sociability was not accompanied by changes in mood of a dysphoric nature as was reported by Rapoport and co-workers¹¹ for d-amphetamine and methylphenidate. Additionally, no physical and/or psychological side effects were reported and observed by any HK child while on ACTH 4-9 analog.

The future implications of these findings for studies with ACTH 4-9 analog suggest that single case studies methodology¹² with a time-series orientation¹³ is warranted.

Acknowledgments

The authors wish to thank Drs. Jean-Paul Bouchard, André Côté, and Faudry Pierre-Louis for clinical support; Ken Laprade, Ginette Pharand-Lefebvre and Louise Blais for technical assistance; and R. Sawdon, N. LeQuéré and G. Savoie-Durette for secretarial assistance. They also thank the Scientific Development Group, Organon International B.V., Oss, The Netherlands, for supplies of ACTH 4-9 analog and for financial support.

References

- MILLER, L.H., KASTIN, A.J., SANDMAN, C.A., FINK, C.A., VAN VEEN, W.J. (1974) Polypeptide influences on attention, memory and anxiety in man. *Pharmacol Biochem Behav* 2:663-8.
- GAILLARD, A.W.K., SANDERS, A.F. (1975) Some effects of ACTH 4-10 on performance during a serial reactions task. *Psychopharmacologia* 42:201-8.
- GAILLARD, A.W.K., VAREY, C.A. (1977) Some effects of Org 2766 on various performance tasks. Institute for perception TNO (Technise Natuur Onderzoeken) report, Netherlands.

4. O'HANLON, J.F., FUSSLER, C., SANCIN, E., GRANDJEAN, E.P. (1982) Efficacy of an ACTH 4-10 analog, relative to that of a standard drug (d-amphetamine) for blocking the "vigilance decrement" in men. Cited in Pigache RM. A peptide for the aged? In: Wheatley D, ed. Basic and clinical studies. Oxford: Oxford University Press, 67-96.
5. American Psychiatric Association. (1980) Diagnostic and statistical manual of mental disorders, 3rd ed. Washington, DC: American Psychiatric Association.
6. KNIGHTS, R.M., HINTON, C.C. (1969) The effects of methylphenidate on the motor skills and behavior of children with learning problems. *J Nerv Ment Dis* 148:643-53.
7. BARKLEY, R.A. (1977) A review of stimulant drug research with hyperactive children. *J Child Psychol Psychiatry* 18: 137-65.
8. BARDLEY, R.A., JACKSON, T.L. (1977) Hyperkinesis, autonomic nervous system activity and stimulant drug effects. *J Child Psychol Psychiatry* 18:347-57.
9. HILL, M.A. (1979) BMDP Statistical Software, Dept. of Biomathematics, UCLA, Los Angeles, California, P2V.
10. BUTTER, H.J., LAPIERRE, Y.D. (1975) The effect of methylphenidate on cardiovascular sensory differentiation on the hyperkinetic syndrome. *Int J Clin Pharmacol* 11(4): 309-14.
11. RAPOPORT, J.L., BUCHSBAUM, M.S., ZAHN, T.P., WEINGARTNER, H., LUDLOW, C., MIKKELSON, E.J. (1978) Dextroamphetamine: cognitive and behavioral effects in normal prepubertal boys. *Science* 199:560-3.
12. REVUSKY, S.H. (1967) Some statistical treatments compatible with individual organism methodology. *J Exp Anal Behav* 10:319-30.
13. KRATOCHWILL, T.R., BRODY, G.H., PIERSEL, W.C. (1979) Time-Series Research: Some comments on design methodology for research in learning disabilities. *J Learning Disabilities* 12(4):52-8.

Inquiries and reprint requests should be addressed to:

Dr. H. J. Butter
CH Pierre-Janet
20 Pharand Street
Hull, Québec
Canada
J9A 1K7