Therapeutic efficacy of a novel transdermal delivery system for (+)-PHNO in Parkinsonian squirrel monkeys

Sir: Serious difficulties in the management of progressive debridement in advanced Parkinson’s disease are caused by diminished benefit from levodopa (“wearing-off” effect) and sudden, unpredictable swings in neurological status (“on-off” effect). These conditions usually do not respond to conventional antiparkinsonian therapy, and indeed may develop as a consequence of nonphysiological, pulsatile stimulation by short-acting dopamine agonists.1 Recently, dramatic improvements in motor fluctuations have been reported following continuous intravenous or subcutaneous infusion of levodopa, lisuride, or apomorphine.2,3 These findings have generated great interest in the development of novel drug delivery systems capable of maintaining stable plasma drug concentrations in the therapeutic range over prolonged periods. A particularly convenient, non-invasive, painless and obtrusive way to achieve this is by transdermal absorption through a rate-controlling membrane. Only a relatively small number of highly potent substances are capable of reaching therapeutic plasma concentrations by the transdermal route (for example, “Transderm-Scop” (Ciba-Geigy) for the treatment of motion sickness). Prior to the recent development of the selective naphthoxazinide D-2 agonist (+)-PHNO, use of such a system for antiparkinsonian therapy has not been possible. Acute oral or subcutaneous administration of (+)-PHNO is capable of fully reversing Parkinsonism in MPTP-treated primates.4 The apparent ease of cutaneous absorption of this potent dopamine agonist on experimental and accidental exposure raised the possibility that (+)-PHNO might be a suitable candidate for transdermal antiparkinsonian therapy.5 We now report our preliminary findings using a rate-controlled transdermal delivery system designed to deliver therapeutic quantities of (+)-PHNO for at least a 24 h period in Parkinsonian squirrel monkeys.

Seven squirrel monkeys were rendered Parkinsonian following treatment with the neurotoxin 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP). Locomotor activity, as assessed by the number of interruptions of photocell units mounted on the animals’ cages, was reduced to around 30% of normal levels after treatment with MPTP. Acute subcutaneous administration of (+)-PHNO (1–20 µg/kg) caused a dose-related increase in locomotor activity which reached normal levels during a 1 h period using a dose of 2.5 µg/kg subcutaneously.

The transdermal drug delivery system had the appearance of a thin adhesive plaster and was comprised of an outer covering membrane, a drug reservoir of (+)-PHNO as free base, a membrane to provide rate-controlled drug release, and an adhesive contact surface. The release rate of drug from this system was estimated to be 2.6 µg/cm²/h in vitro. Transdermal patches

<table>
<thead>
<tr>
<th>Table</th>
<th>Plasma concentrations of (+)-PHNO (µg/ml) in a single squirrel monkey following application of transdermal patches covering a skin surface area of 2.4 or 9.6 cm².</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin surface area (cm²)</td>
<td>Time after patch application (h)</td>
</tr>
<tr>
<td></td>
<td>4</td>
</tr>
<tr>
<td>2.4</td>
<td>53</td>
</tr>
<tr>
<td>9.6</td>
<td>115</td>
</tr>
</tbody>
</table>

References


CA MANGONE
E HERSKOVITS*
Neurology Unit,
Hospital Juan A Fernandez Cerviño,
Buenos Aires, Argentina.

*Deceased 5 March 1988

Address for correspondence: Dr Carlos A Mangone, Hospital D F Santojanni, Neurolagia, Pilar 950 (1408), Buenos Aires, Argentina.
covering an area between 2-4 and 19 cm² were applied to the shaved chests of Parkinsonian monkeys. Locomotor activity was increased according to the skin surface area available for transdermal absorption, and was restored to the range observed in normal, untreated monkeys throughout a 24 h period using a surface area of 4-9-19 cm². Comparing the minimum dose of (+)-PHNO required for restoration of locomotor activity to normal levels by the subcutaneous and transdermal routes (2-5 µg/kg/h and 4-78 cm², respectively), we would estimate the systemic availability of (+)-PHNO using the transdermal patch to be ≤20% of the in vitro release rate. Analysis of plasma levels of (+)-PHNO in a single animal treated with transdermal patches covering an area of either 2-4 or 9-6 cm² indicated a lag period of approximately 12 h before stable plasma levels were attained; thereafter plasma concentrations of (+)-PHNO remained stable throughout the following 36 h period until the patches were removed at 48 h. Steady state plasma levels of (+)-PHNO were proportional to the surface area of skin exposed to the transdermal delivery system (approximately 100 pg/ml using a patch size of 2-4 cm², and 500-600 pg/ml for a total patch size of 9-6 cm², table).

Our findings indicate that plasma levels of (+)-PHNO within the therapeutic range may be achieved and sustained for at least 24 h using rate-controlled transdermal absorption, and suggest a novel sustained release delivery system for antiparkinsonian therapy.

N M J RUPNIK, S J TYE, C A JENNINGS A E LOPER,* J V BONDI,* M HICHENS* S D IVERSEN, S M STAHL

Merck Sharp & Dohme Research Laboratories, Neuroscience Research Centre, Terlings Park, Harlow, Essex, CM20 2QR, UK, and Merck Institute for Therapeutic Research, Merck Sharp & Dohme Research Laboratories,* West Point, Pennsylvania, USA.

References

8 Jenner P, Marsden CD, Nomoto M, Stahl S. Antiparkinsonian activity of (+)-PHNO in the MPTP-treated marmoset following subcutaneous infusion or skin application. Br J Pharmacol 1986;89:626P.

Accepted 9 October 1988

Matters arising

Herpes simplex type II encephalitis with complete Klüver-Bucy syndrome in a non-immunocompromised adult

Sir: In your issue of March 1988, Baker et al reported the unexpected finding of herpes virus type II (HSVII) as the causal agent of an encephalitis occurring in a young, non-immunocompromised adult. This diagnosis was supported with relevant serological investigations. The patient was treated with intravenous acycloguanosine and gradually recovered with no neurological sequelae except for a long-term memory deficit. Whereas HSVII is the most common cause of acute encephalitis in the neonate, the authors pointed out that in adults, acute necrotising encephalitis is usually due to herpes simplex type I (HSVI). They stated that their report represented “a previously unrecognised entity due to HSVII in a non-immunocompromised adult.”

This last point, however, should be corrected. To our knowledge, two similar cases had already been reported.23 We had the opportunity to observe one of these. A 42 year old, previously well man presented with a 3 day history of fever, diffuse myalgias and intense headache with vomiting. The day prior to admission he became confused and disoriented, and experienced auditory hallucinations. Soon after admission, he became comatose and required endotracheal intubation. Computed tomography showed large areas of low density involving both temporal lobes which showed contrast enhancement. A seroconversion for HSVII was demonstrated in blood and cerebrospinal fluid (CSF) with a rising of specific IgM titre. In blood, the HSVI IgM titre was 1:80 at day 8 of the illness, and 1:1024 at day 16. In CSF, the titre was 1:16 at day 8, and 1:250 at day 16. The patient was treated with intravenous acyclovir for 10 days. His condition slowly improved, allowing formal neuropsychological testing. The typical characteristics of a complete Klüver-Bucy syndrome were demonstrated. The neuropsychological data are published elsewhere. Unfortunately, it was noted 8 weeks after its onset, the encephalitis recurred, and, in spite of a second course of treatment with acyclovir, the patient was left in a demented state. Neither immunocompromise nor a co-existing potentially immunodepressive disorder was able to be demonstrated in our patient. Four years later, the patient is alive and he has been otherwise well.

When we published this case, we were only able to find six other well-documented examples of HSVII encephalitis in adults reported in the literature.2-4 Usually the patients2 were immunodepressed and had genital herpes; however, in one case,2 as in ours, no predisposing factors were found. Since then, in spite of the increasing number of immunocompromised patients with acquired immunodeficiency syndrome (AIDS), only very few cases of HSVII encephalitis, or encephalomyelitis, have been reported in those patients.5 The rarity of HSVII encephalitis in both healthy and immunocompromised patients remains to be explained.

S BACHLINE, F CHAIN, F LHERMITTE
Clinique de Neurologie et Neuropsychologie
Hôpital La Salpétrière
47, boulevard de l’Hôpital
F 75651 Paris cedex 13 (France)

References

Therapeutic efficacy of a novel transdermal delivery system for (+)-PHNO in parkinsonian squirrel monkeys.


J Neurol Neurosurg Psychiatry 1989 52: 289-290
doi: 10.1136/jnnp.52.2.289

Updated information and services can be found at:
http://jnnp.bmj.com/content/52/2/289.citation

Email alerting service

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/