An Alternative Treatment for Parkinson's Disease*

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Parkinson's disease is a degenerative process involving the loss of over 70–80% of the dopaminergic neurons in the substantia nigra [1]. This results in progressive yet variable loss of freedom of movement, dexterity, mechanical ability, and often cognitive capacity. It afflicts people in various periods of their lives; it can devastate the careers and lives of young patients and incapacitate vigorous older, though active, patients [2]. The current standard medical strategies of treatment include medications such as combinations of carbidopa/levodopa, cathechol-O-methyl transferase inhibitors, monoamine oxidase inhibitors, bromocriptine and amantadine. They are administered in an attempt to raise dopamine levels in the central nervous system, thereby replacing the shortfall of dopamine [2,3]. As transfer of systemically delivered dopamine across the blood-brain barrier is severely limited due to polar, steric and physical barriers, the relative overdose of oral carbidopa/levodopa combinations has substantial side effects. The other classes of drugs are often problematic as well. The neurologic, psychiatric, cardiovascular and gastrointestinal effects may be a great impediment to optimal dosing [2]. Additionally, timing can be a grave problem with on/off phenomena making a patient's situation that much more distressing. As patients age, other marginally or unrelated problems beset them, such as spinal stenosis. One of the treatments for the pain of spinal stenosis is epidural steroid injection. Though not a cure, it does provide great relief for many patients and can forestall surgery. We present a case of a patient who was afflicted with both these conditions and was treated in a novel fashion, with surprisingly good results.

Patient Description

An 82 year old woman was referred for moderate lower back pain and leg aching when walking. The difficulty developed over many months, constricting her ability to complete activities of daily living without discomfort. She also had a several year history of Parkinson's disease diagnosed by her neurologist and managed with carbidopa/levodopa. The results were good initially but gradually began to deteriorate, requiring higher doses. She did not tolerate bromocriptine well or other dopaminerigic medications available in 2002–2004. Following physical examination, review of her radiologic studies and our discussion, it was suggested that she undergo epidural steroid injection.

After consent was obtained, the first of these was performed with some improvement in the distance she could walk before she developed pain and heaviness in the legs. It was suggested she undergo a second injection. At this point she felt the absence of pain, revealing that she was quite limited by the movement disorder. She inquired if anything could be tried for the Parkinson's disease while the injections were being done. We informed her that dopamine could be combined with the depo-steroid/bupivicaine, instead of epinephrine, but this was not standard practice and novel for this procedure. She agreed to try, and after consent was obtained the procedure was scheduled and performed. Injection into the epidural space was via the trans-sacral route. The solution injected contained Depo-Medrol® 80 mg, dopamine 20 µg, and bupivicaine 0.125% to a total volume of 20 ml. There were no complications technically or hemodynamically; she was discharged as with her prior injection after less than 2 hours. During the day she felt much better with less pain and was much more mobile. She had minimal resting tremor, a more solid gait, and more expressive facial appearances while on the same oral regimen of levodopa/carbidopa. She was lost to follow-up after 8 weeks with sustained improvement.

Comment

The reasons for improvement appear to be:

- Direct access to the central nervous system bypassing the blood-brain barrier. In this fashion the issue of overdosing systemically to overcome the blood-brain barrier is negated. The patient suffers no ill effects from the systemic administration of levodopa or other medications. As with local anesthetics, oral dopamine is not effective at the site of action. Epidural and intrathecal administration of medication for pain and spasticity has been standard practice for many years. It includes long and short-term infusions [4]. It should be noted that dopamine has not been approved by the Food and Drug Administration for intrathecal or epidural administration and this was an off-label use. The complications of administration of dopamine via the epidural space are the same as those of epinephrine via the epidural space. Inadvertent intravascular administration could lead to a short period of hypertension and tachycardia with their attendant

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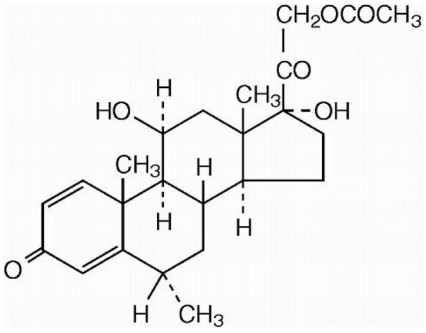
problems. Though quite unlikely from the trans-sacral approach, inadvertent subarachnoid and subdural injection would likely mimic the distribution and effect of epinephrine in the same spaces; that is to say, probably little hemodynamic effect and possibly some patchy anesthesia at various levels.

- Mixing the dopamine in a vehicle containing a compound known to retard absorption (Depo-Medrol). The whole premise under which epidural steroid injection is undertaken rests on the notion that any significant inflammatory change present at the nerve root is suppressed by the steroid; the longer the exposure to the steroid the longer the anti-inflammatory effect. To accomplish this with any steroid that is chemically primed for easy absorption and removal from the site where it is actively needed requires compounding it with a vehicle that retards absorption. The matrix used to lengthen the duration of absorption of the methylprednisolone is proprietary, though it has recently been reformulated to extend the duration of absorption. The matrix is capable of harnessing a steroidal compound with the following structure [Figure]:
- Our hypothesis was that the same matrix would retain catecholamines that have a similar, though more basic steroidal structure. It appears that it does.
- A large repository of drug in comparison to the amount needed for function – 20 µg deposited vs. femtogram quantities needed at the receptor sites. The minute amount of dopamine needed to maintain near normal activity is what allows the oral overdosage, with the immense first-pass effect, to supply a very small amount of dopamine to the neostriatum. Imagine how beneficial it would be if a large repository of dopamine was resident in the central nervous system and percolated through the cerebrospinal fluid to reach the under-stimulated neostriatum on a continuous basis; this would allow dramatic long-term improvement
- A delivery system from the repository to the active site – slow diffusion into the cerebrospinal fluid and possibly via the valve-less Batson's plexus. This would imply several useful possibilities which may not be mutually exclusive: a) periodic epidural injection with a matrix that would restrict the release of dopamine over extended periods, similar to what is now used for steroids as well as narcotics and (experimentally) local anesthetics; b) an indwelling pump/reservoir/catheter combination such as is currently used for intrathecal delivery of opiates and baclofen, and c) caudal injection of a native cellular or stem cell line that has been hybridized to secrete dopamine.



Methylprednisolone

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Capsule

Smaller families are better for survival

Fitness, defined as an individual's reproductive success, is measured by the number of offspring, and parents with more offspring are generally considered fitter. However, Penn and Smith show that in married couples in pre-industrial societies, the survival of both the mother and the father depended on the number of offspring the wife had, and families with fewer children had more surviving grandchildren. In an analysis of 21,000 records of survival in late 19th century Utah in the USA, survival rates of the parents and children were significantly lower in the largest families, that is, those with 12 or more children. The negative effect of bearing children on fitness was stronger in females, lasted after menopause, and was evident even in women with only 1 to 3 offspring. However, after the birth of the fourth child, the risk of death became significantly greater in fathers, too. In addition, those children with the largest number of siblings were less likely to survive to the age of 18, with the youngest siblings at greatest risk. The ability of human females to survive long after the loss of reproductive function has previously been explained by the positive effect a mother's survival has on the success of her offspring; without a mother, survivorship of the children is lowered. Nevertheless, this study demonstrates that there may be a selective pressure for females to stop reproducing before they complete child rearing.

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