Cerebroventricular clozapine would be a viable treatment modality for clozapine-dependent schizophrenia patients with neutropenia

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The atypical antipsychotic clozapine is very effective for treatment of schizophrenia, but it causes agranulocytosis requiring drug cessation in up to 2% of cases. There has been some success rechallenging with clozapine at a later date or giving granulocyte colony stimulating factor or lithium while continuing clozapine. However, there are still some patients for whom these strategies do not work yet who cannot be controlled on other medications. This paper proposes that for such individuals, cerebroventricular administration of clozapine via Ommaya catheters could allow continued use of clozapine therapy. Direct infusion into cerebrospinal fluid means far smaller amounts of drug would be needed for efficacy, and clozapine concentrates in the central nervous system where it would not be exposed to bone marrow stem cells to cause agranulocytosis. This treatment paradigm would also provide a means for court-ordered clozapine therapy and a possible delivery system for future therapeutics based on trophic factors such as brain-derived neurotrophic factor.

Background

The atypical anti-psychotic drug clozapine has had a unique niche in the treatment of schizophrenia for over 30 years. Some patients respond only to clozapine, especially for negative symptoms of schizophrenia resistant to most other medications [1]. Clozapine carries risks of various side effects, including seizures, myocarditis, urinary incontinence and suppression of neutrophils and granulocytes [2]. Up to 2% of patients eventually manifest agranulocytosis or neutropenia that can be fatal if clozapine is not stopped, and some do not do well on other drugs, even newer atypical antipsychotic agents such as quetiapine and olanzapine. The plight of clozapine-dependent patients has prompted attempts at clozapine rechallenge, but there are still some patients who have to be taken off clozapine the second time it is tried. As an example, in a series of 53 patients rechallenged with clozapine after a first episode of neutropenia, a total of 20 (38%) had repeat agranulocytosis [3]. For a few other patients, clozapine has been continued in the face of ongoing agranulocytosis by administering either granulocyte colony stimulating factor (GCSF) to increase proliferation of neutrophils or lithium carbonate which stimulates migration of mature neutrophils into the circulation [2,4,5]. However, neither strategy is always successful. For example, in one case report where GCSF failed to reverse clozapine-induced agranulocytosis, the patient had to discontinue clozapine and be placed permanently in a psychiatric hospital [6].

Presentation of the hypothesis

For patients who otherwise face a choice between life-threatening complications from clozapine and lifetime placement in a psychiatric hospital, it is proposed here the hypothesis that cerebroventricular administration of clozapine via indwelling Ommaya catheters would allow continued use of clozapine therapy free of side effects. Basic science data indicates that the amount of clozapine needed for control of schizophrenia should be much less if clozapine were directly delivered into cerebrospinal fluid. Cerebrospinal fluid sampling of patients on therapeutic doses of clozapine show that they have a steady state concentration of approximately 20 ng/ml [7]. Total cerebrospinal fluid volume is approximately 250 ml [8]. This means that a total of 1000 ng (1 µg) would have to be infused into the CSF volume over some defined period of time to reach steady state. Clozapine preferentially accumulates within the central nervous system even from peripheral administration. Following intraperitoneal injection of clozapine in rats, the concentration in the brain was 24 times serum concentration [9], so serum clozapine from cerebroventricular administration should be a small fraction of the cerebrospinal fluid concentration and well below the threshold for causing neutropenia and cardiomyopathy, especially since the total dose of clozapine is so much lower (1 µg in a dosing interval to be worked out, versus up to 900 mg...
per day at a time for typical oral administration). If we assume the 1:24 ratio of serum to CSF clozapine at steady state, this works out to only 40 ng of clozapine in the serum compartment, and any adverse effects in bone marrow and heart should be nil. However, side effects originating within the central nervous system may require specific countermeasures. For example, clozapine-induced seizures have been reported from oral clozapine, but these seizures have been successfully treated with anti-epileptic medications such as gabapentin, carbamazepine, valproic acid and phenytoin [2,10,11].

Urinary incontinence too could be a problem with direct infusion of clozapine into cerebrospinal fluid, perhaps even worse than with current oral administration, as studies in rats indicate clozapine-induced enuresis and incontinence originates in the spinal cord rather than the bladder following either cerebroventricular or lumbar infusion [12]. But this side effect should also be surmountable with adjunctive medications such as vasopressin, oxybutynin, bethanechol and ephedrine, which have proven effective for urinary symptoms from oral clozapine [13–15].

Assuming side effects of cerebroventricular clozapine are manageable, Ommaya intraventricular catheters implanted into cerebral ventricles by neurosurgeons or interventional radiologists provide a proven means for drug delivery. For example, a child with central nervous system lymphoma was failing intravenous retuximab, but when the retuximab was administered via an Ommaya catheter at lower concentrations, there was complete regression of the lymphoma [16]. Ommaya catheters have also been successfully used to deliver methotrexate for central nervous system lymphoma, isoniazid for tuberculous meningitis and amphotericin for coccidoidal meningitis [17–19]. In all of these applications, the aim was to get high concentrations in brain for maximum efficacy and minimum side effects outside the brain, exactly the scenario here. The Ommaya pump is entirely percutaneous, with no external attachments. The drug reservoir of an Ommaya catheter sits under the scalp for easy access, and a patient only has to be aware to seek medical attention for prolonged headaches, fever or loss of distensibility of the drug reservoir but otherwise has no lifestyle restrictions. The Ommaya catheter is perhaps the only viable means for direct central nervous system delivery of clozapine, which is a lipophilic drug [20]. Lipophilic drugs injected into the lumbar intrathecal space are cleared from the cerebrospinal fluid before they can reach the cistern magna [21]. Therefore, a lumbar intrathecal pump would not deliver clozapine to where it is needed, whereas the Ommaya would release it directly into the cerebral cortex and basal ganglia.

Validating the hypothesis

Acute short-term administration of intraventricular clozapine has already been accomplished in rats using cerebroventricular pumps comparable to Ommaya catheters for humans [12]. To carry this idea forward, proof-of-principle with chronic cerebroventricular infusion of clozapine should also be done with rats, to prove that serum and bone marrow concentration of clozapine following cerebroventricular administration is minimal and also to find out the drug half life in this setting. The half life orally administered clozapine is about 6 h [22], but the pharmacokinetics might be quite different with direct infusion into cerebrospinal fluid.

Once this is completed, clinical trials could commence for clozapine-dependent schizophrenia patients with neutropenia or other potentially lethal side effects who have failed clozapine rechallenge alone and clozapine rechallenge with lithium and GCSF. The number of patients worldwide in this category would be small, but the research and development costs to carry this out would be relatively low, since Ommaya catheters are already commercially available. It may be desirable to have interventional radiologists give a test dose of cerebroventricular clozapine into the lateral cerebral ventricles, using as a model a case history of CT guided cannulation of the lateral ventricular to administer methotrexate for central nervous system lymphomas [23]. Those who have good control of schizophrenic symptoms could then be referred for implantation of Ommaya pumps.

Implications of the hypothesis

The proposal here could have immediate benefit for clozapine-dependent schizophrenics with agranulocytosis. Furthermore, cerebroventricular administration of drugs via Ommaya catheters might have important implications for schizophrenia treatment and research far beyond this original target population. Ommaya delivery of clozapine would offer a means of insuring court-ordered medication compliance, as the reservoir could be filled every week or every month in an outpatient setting. As of now, there is no depot form of clozapine comparable to that for haloperidol and risperidone. Perhaps most importantly, this proposed drug delivery method opens the door to future treatment of schizophrenia through infusing trophic factors such as brain derived neurotrophic factor (BDNF). Emerging research suggests that deficiencies of trophic factors like BDNF are involved in the pathogenesis of schizophrenia, especially treatment resistant schizophrenia [24,25]. If administering BDNF itself can alleviate schizophrenia, Ommaya catheters would be a practical way to accomplish this, and they would allow frequent noninvasive sampling of cerebrospinal fluid for pilot studies and ongoing therapy. This idea is thus respectfully put forward here for the potential benefit of psychiatrists, researchers and patients around the world.

Conflict of interest statement

None declared.

References


