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Intraventricular vancomycin in the treatment of ventriculitis associated with cerebrospinal fluid shunting and drainage

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SUMMARY The results of treatment of 50 cases of ventriculitis associated with the use of cerebrospinal fluid shunts or external ventricular drains, and treated with intraventricular vancomycin, are reported. While the overall cure rate was 66% with four cases lost to follow-up, in those cases where treatment involved shunt removal, 20 mg vancomycin daily intraventricularly, and another appropriate systemic antibiotic, 22 of 24 cases were cured with two cases lost to follow-up. In those cases where the shunt was left in during treatment, results were poor and revision for blockage of the distal catheter of ventriculoperitoneal shunts was required in 44% of these. All five patients whose ventriculitis followed external ventricular drainage were cured. Despite relatively high trough levels of vancomycin in the cerebrospinal fluid, no evidence of toxicity was seen.

Infection is a major cause of failure of cerebrospinal fluid (CSF) shunting devices used to control hydrocephalus. The reported incidence varies from 1% to 39%,[1 2] with a national average of around 10% of operations. Similarly, external ventricular drainage, either as a temporary measure to control hydrocephalus or in order to manage raised intracranial pressure following, for example, subarachnoid haemorrhage, is also frequently associated with ascending infection resulting in ventriculitis. The organisms involved are predominantly gram-positive with coagulase-negative staphylococci being the most common.

While many attempts have been made to eradicate shunt infections without removal of the shunt these have met with little success and it is now generally accepted that effective treatment should involve removal of the shunt and the use of appropriate antimicrobial chemotherapy.[3] However, even after the shunt has been removed ventriculitis may persist despite intravenous antibiotics. Ventriculitis caused by gram-positive organisms commonly gives rise to low neutrophil counts and low protein concentrations in the CSF, indicating only a mild inflammatory response. This leads to difficulties in achieving and maintaining adequate therapeutic drug levels in the CSF[4] using intravenous regimens. Antimicrobials, and particularly gentamicin, have therefore been administered intraventricularly, with some success. The increasing resistance of coagulase negative staphylococci to gentamicin prompted us to consider the use of vancomycin, to which all strains have so far proved susceptible.[5] Unfortunately, intravenous administration of vancomycin gives poor CSF levels in the absence of a strong inflammatory response,[6 7] and consequently the drug has been administered intraventricularly in six patients.[8–12] We have also reported preliminary experience with the use of intraventricular vancomycin in 10 cases,[13] and we present here further data on those cases along with 40 others.

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Patients and methods

Forty-six patients received intraventricular vancomycin in 50 separate episodes. Their ages ranged from one month to 63 years with 17 less than ten years; 11 of these patients were less than one year old at the time of treatment. The underlying pathologies included spina bifida (11), primary infantile hydrocephalus (10), subarachnoid haemorrhage (4), aqueduct stenosis (3), intracranial tumour (5), cyst of the third ventricle (3), post haemorrhagic infantile hydrocephalus (3) and seven others represented by single cases. These included one case of cerebral sarcoid and one of cere-

bral cysticercosis.

At the time of diagnosis of infection, 28 had ventriculoperitoneal (VP) shunts, 12 had ventriculoatrial shunts, four ventriculopleural and one cystoperitoneal. Five cases occurred without a shunt but in association with an EVD.

Microbiological diagnosis was made by finding organisms in the gram film and culture of ventricular CSF. The CSF neutrophil count immediately before beginning intraventricular vancomycin was recorded in 44 cases. In 35 of these cases due to coagulase negative staphylococci alone, it ranged from 5/mm^3 to 2000/mm^3, but in only three cases were counts in excess of 400/mm^3. All four cases due to *Staphylococcus aureus* had counts greater than 4000/mm^3.

Forty episodes were due to coagulase negative staphylococci, three to enterococcus, two to *S. aureus*, two to both *S. aureus* and coagulase negative staphylococci and one each to *Propionibacterium acnes*, an unidentified coryneform and *Streptococcus sanguis*. In all cases the organisms were susceptible to vancomycin on conventional testing. In 27 cases antimicrobials had already been administered, intraventricularly in 13, in an unsuccessful attempt to treat the infection. Surgical treatment for infection varied between surgeons and between hospitals. In 16 cases the whole shunt was removed as soon as infection was diagnosed and an extraventricular drain inserted, while in a further three cases an Ommaya reservoir was inserted instead of the drain. In 17 cases the distal end of the infected shunt was exteriorised but the shunt was then left in place for most of the duration of the vancomycin therapy. In nine cases the shunt was not removed as part of the management of the infection. In five cases no shunt was used, infection developing during the use of an extraventricular drain.

The standard intraventricular daily dose of vancomycin was 20 mg and this was given in 38 cases. However, in some cases a smaller dose was given, so that one patient received 15 mg, five patients received 10 mg and six patients received 5 mg daily. The drug was given daily for periods varying from 3 to 38 days (median 8 days). The drug was diluted aseptically in sterile water for injection or sterile saline solution and finally passed through a bacterial filter. The doses were made up in a 2 ml volume and injected into the shunt reservoir or into the injection port of the extraventricular drain clamping distally or into the separate reservoir, as available. Rifampicin was given either orally or intravenously in 23 cases. Vancomycin was given intravenously in seven cases. Intraventricular vancomycin was the only antimicrobial administered in eight cases. In the remaining cases various drugs such as fusidic acid or a cephalosporin accompanied the intraventricular vancomycin. CSF vancomycin levels were measured in 25 patients by fluorescence polarisation (TDX ABBOTT, UK). Follow-up after treatment varied from 4 months to 3 years (median 11 months), except for those patients whose infection relapsed before this period or who did not respond to treatment and four patients who were lost to long term follow-up. In the event of shunt revision being required during follow-up, note was made of microbiological results of examination of CSF and removed catheters, and every other opportunity was taken to examine CSF during this period. For the purposes of analysis, results within one month of stopping treatment (short term follow-up) were noted, but definitive results were recorded after longer term follow-up as above.

Results

None of the patients exhibited signs of acute toxicity or irritation during intraventricular administration of vancomycin. Only one patient experienced a systemic reaction ("Red Man syndrome"). It had been intended that this patient should receive the drug both intraventricularly and intravenously, but the reaction occurred during the first intravenous dose. The intravenous administration was therefore stopped but the drug continued to be given uneventfully by the intraventricular route. No renal or eighth nerve toxicity due to vancomycin was noted in any of the patients, though six patients were found to exhibit eighth nerve dysfunction at review after they had recovered from the infection and had been discharged. Four of these had ataxia, one was deaf, and one was both deaf and ataxic. In four of the ataxic patients including the one who was also deaf, the eighth nerve dysfunction had been noted before the infection for which vancomycin was given. This was also true of the patient who showed only deafness, which had followed administration of streptomycin for tuberculosis in another country. In the remaining patient the ataxia appeared a few weeks after vancomycin therapy. He was subsequently found to be suffering from phenytoin toxicity and his ataxia improved on adjusting the dose.

Trough CSF levels of vancomycin were measured 24 hours after at least two, and not more than five, doses in 25 patients. These ranged from 5 mg/l in one case to 236 mg/l in another (median 26·8 mg/l). Peak CSF levels were measured in seven cases, within four hours of administration, and these ranged from 26 mg/l to 280 mg/l. Two levels of >1000 mg/l were recorded but these were from samples taken from the distal end of the extraventricular drain and probably represented drugs which had failed to enter the ventricular system and had instead escaped down the drainage tube.

Five patients had an extraventricular drain at the time of their infections. All received 20 mg of vancomycin and all recovered without relapse.

The remaining 45 patients had shunts in place when their infection was diagnosed. Of these, 28 cases (62%) were cured of their infections, though a further four were followed only for between two and two and a half months before returning to their country of origin and becoming unavailable for further follow-up. The treatment regimes were retrospectively arranged into five groups for analysis, and the table shows the results related to treatment group. In Group 1, patients had shunt removal soon after diagnosis of infection, followed by 20 mg of vancomycin injected daily intraventricularly and either oral or intravenous rifampicin. In this group there was one relapse soon after stopping treatment, but in this case a

Table *Results of treatment*

Treatment	*N*	*Eradication of Infection:* *Short-term*	*Long-term*	*No response/ early relapse*	*Late relapse*	*Revision for blockage within 4 months*
Shunted patients						
Group 1	14	13	11 (+2 lost to follow-up)	1	0	1
Group 2	10	9	9	1	0	0
Group 3	7	4	3 (+1 lost to follow-up)	3	0	0
Group 4	5	2	2	3	0	0
Group 5	9	5	3 (+1 lost to follow-up)	3 (+1 secondary infection)	1	4
Non -shunted patients						
(EVD)	5	5	5	0	0	0
Overall	50	38 (76%)	33 (+4 lost to follow-up) (66%)	11 (+1 secondary infection)	1	5

Group 1: Had 20 mg vancomycin, rifampicin and shunt removal.
Group 2: Had 20 mg vancomycin, a systemic antibiotic other than rifampicin and shunt removal.
Group 3: Had less than 20 mg vancomycin, rifampicin or another antibiotic, and shunt removal.
Group 4: Had vancomycin and shunt removal but no other antibiotic.
Group 5: Kept their shunts in throughout treatment.
Short term follow-up was for up to one month after stopping treatment. Long term follow-up was for between four months and three years (median 11 months).

further course was given with complete success. One patient required revision of the new VP shunt within 4 months of stopping treatment, but the CSF and removed shunt grew no organisms. This patient had cerebral sarcoid. Nine of the 10 patients in Group 2 who were treated in the same way as Group 1 cases except that an antibiotic other than rifampicin was given, recovered completely. In the tenth case, a short four-day course of vancomycin given both intraventricularly and intravenously was followed by relapse though successful eradication was achieved after a further ten-day course. If the two re-treated cases are included in the successes, the cure rate for patients in Groups 1 and 2 is 92%, with the remainder consisting of two cases who were not available for long term follow-up.

The seven patients in Group 3 had 5, 10, or 15 mg of vancomycin daily intraventricularly, along with either rifampicin or another antibiotic to which the organism was susceptible in vitro, and shunt removal. Two patients relapsed during or within a few days of stopping treatment and one showed no response. The remaining three had their infections eradicated, with one lost to follow-up. Of the five patients in Group 4 who had their shunts removed and received intraventricular vancomycin but no other antimicrobial, two had their infections successfully eradicated. Of the remainder, one showed no response and two relapsed within 3 weeks of stopping treatment.

The nine patients in Group 5 did not have their shunts removed or exteriorised as part of the treatment. Three patients had their infections eradicated but five relapsed after stopping treatment, and one succumbed to a *S aureus* ventriculitis following apparent eradication of her *S epidermidis* infection and later reshunting. All organisms were compared by means of antibiogram and biochemical profile using API Staph (API UK Ltd). One patient was followed up for only three months before returning to his country of origin. The five patients who contracted their infections while on extraventricular drain all showed complete recovery. Four of these were due to coagulase negative staphylococci and one was due to *S. aureus*. Of the 33 patients who were cured of their infections, 23 were reshunted using the ventriculoperitoneal route, and a further five received ventriculoatrial shunts.

There was no significant difference in cure rate on long term follow-up between the 21 cases who became apyrexial within 3 days (76%), the 10 cases who remained pyrexial for more than 3 days (60%) or the 19 cases who were never pyrexial (74%). However, when the time taken for organisms to disappear from gram film and culture of CSF were examined, in the 45 cases where these data were available, 31 were seen to have responded by day 3 and 14 took longer. In the first group the long term cure rate was 81% whereas in the second it was 36% ($\chi^2 = 6{\cdot}856$, $p < 0{\cdot}05$).

Discussion

Vancomycin is active in vitro against staphylococci, coryneforms and most streptococci, including most enterococci. It is therefore a potentially valuable antibiotic for use in implant-associated infections, but therapeutic levels are difficult to achieve in ventriculitis due to gram positive organisms because of the

usually mild inflammatory response. This led Visconti *et al* to administer the drug intraventricularly to a two year old boy.[10] The dose used was 20 mg daily for 3 days, and this led to eradication of the infection which previous treatment, including intraventricular gentamicin, had failed to do. Eighteen of the 33 cases reported here in which the use of intraventricular vancomycin led to eradication of infection had had previously unsuccessful courses of treatment, half of them receiving antimicrobials intraventricularly. Young *et al* using 20 mg daily for 10 days, successfully treated *S aureus* ventriculitis in a 60 year old.[11] Raoult *et al* initially used intravenous cefotaxime and intraventricular amikacin in their case, but without success, which was only achieved after giving vancomycin both intravenously and intraventricularly (50 mg daily) for 15 days.[8] In a preliminary report of the first 10 cases in this study we used 20 mg of vancomycin daily intraventricularly with success in eight cases.[13] Intraventricular vancomycin has also been used successfully in cases of enterococcal meningitis or ventriculitis.[15] In the case reported by Young *et al,*[11] vancomycin was initially given only intravenously, but despite a serum level of 92 mg/l, 15 minutes after a dose of 500 mg, CSF levels never rose above 6 mg/l. Following intraventricular administration, however, CSF levels ranged from 5–50 mg/l (median 19 mg/l). CSF levels were also measured in another study and were found to be greater than 100 mg/l on two occasions.[16] In addition, CSF levels ranging from 29 mg/l to 119 mg/l have been reported after inadvertent administration of 45 mg vancomycin.[14] In none of these cases has any toxicity been reported, and the drug appears to be safer for intraventricular use than gentamicin in that arachnoiditis and radiculopathy[15] and seizures[17] have been reported when high doses of gentamicin were used.

A standard dose of 20 mg daily was used in 38 of our cases with lower doses of 5–15 mg in the infants. For intraventricular use, the dose of a drug should not be based on body weight or age, but on ventricular volume. However, this is not often known and though it is possible to calculate it accurately the opportunity is rarely afforded and a recent CT scan enables an assessment to be made which is probably sufficient. The success rate in Group 3 was not as high as in Groups 1 and 2. The duration of treatment should be determined by bacteriological and clinical response. From our results we would recommend that intraventricular vancomycin should be given until organisms can no longer be detected on microscopy or culture, then for 3 or 4 days longer, with the last dose being given on the day of reshunting where this is necessary. It appears that, if bacteriological clearance is not achieved by day 3 or 4 of treatment, then the chances of eventual success are significantly diminished.

Patients in Group 1 received rifampicin in addition to intraventricular vancomycin. This drug combination has been shown to be effective in prosthetic valve endocarditis[18] and in meningitis[12] and shunt infection.[19] Patients in Group 2 received a drug other than rifampicin in addition to intraventricular vancomycin. In some cases this was intravenous vancomycin, but the incidence of problems with peripheral venous access caused us not to favour the administration of vancomycin by this route when the organism was susceptible to another appropriate drug. There appeared to be no difference in cure rates between Groups 1 and 2. However, while the number of patients in Group 4 does not allow statistical comparison, it is probable that the administration of either rifampicin or another appropriate agent systemically with intraventricular vancomycin is beneficial. Certainly this is advisable in view of the fact that, in the presence of a shunt, the organisms causing ventriculitis are disseminated extracranially.

For obvious reasons, many attempts have been made to eradicate infection in a functioning shunt without resorting to its removal. However, the results have not been encouraging, and this has recently been confirmed by James *et al.*[3] The results in the nine cases reported here where the shunt was retained during antibiotic treatment also confirm this in two respects. Firstly only three were shown to have had their infections eradicated on long term follow-up, and one of these had been caused by *S sanguis,* an organism which might be more easily eradicated from shunts and catheters than coagulase negative staphylococci. Secondly, of the seven cases where the shunt drained into the peritoneal cavity, four underwent revision for distal end blockage within four months of stopping treatment, despite three of these having had their infections successfully treated. An increase in revisions for distal catheter blockage in peritoneal shunts after successful non-surgical management of shunt infection, and two cases of bowel perforation by the distal catheter, led us to abandon this form of treatment in a previous study (Bayston *et al,* unpublished results). The cause of the blockage is probably encystment of the lower catheter in the peritoneal cavity occurring either before or during treatment, resulting in occlusion of the lower catheter and its fixation to the peritoneum. Fixation probably increases the likelihood of perforation of bowel whose serosal surface remains thickened and somewhat friable following the infection.

From the study we conclude that vancomycin is safe for intraventricular use in ventriculitis due to gram positive bacteria, and that if the extraventricular drain or shunt is removed, and 20 mg vancomycin is given daily intra-ventricularly for 3 or 4 days beyond

beyond the last day on which organisms are still present in the ventricular CSF, along with an effective systemic or oral antimicrobial, then successful eradication can be expected in over 90% of cases at the first attempt.

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