Treatment of Herpes Simplex Encephalitis

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Herpes simplex encephalitis was first established as a specific entity by Smith et al. (1941) who identified intranuclear inclusion bodies in nerve cells and isolated herpes simplex virus from brain tissue from a four-week-old child who had died of encephalitis. In 1956, Dodge and Cure reported the first case in which the diagnosis of encephalitis with intranuclear inclusion bodies was established during life by brain biopsy. Since that time an ever-increasing number of publications have described the clinical features and pathology of herpes simplex encephalitis. The mortality rate has been high, from 70 per cent (Olson et al., 1967), to 90 per cent (Dudgeon, 1970). Until recently the disease was considered untreatable and there still remains considerable doubt as to whether any therapeutic measures are, in fact, of benefit. Despite claims made for the therapeutic effect of steroids, their use has remained controversial and the only potentially specific therapeutic agent described in the treatment of herpes simplex encephalitis is idoxuridine. The first reports of successful treatment with this drug were those of Breeden et al. (1966) and Evans et al. (1967) and in all there are some 25 cases of treatment with idoxuridine reported in the literature. Most of the reports have been of single cases.

During an analysis of the literature on herpes simplex encephalitis (Illis and Merry, in preparation) it became apparent that there was a considerable difference between the mortality of untreated cases of herpes simplex encephalitis and those treated with idoxuridine. The purpose of this article is to evaluate the relevant data concerning the methods of treatment of herpes simplex encephalitis, to emphasise the potential benefits of idoxuridine treatment, and to put the toxic effects of such treatment into perspective.

CLINICAL MATERIAL

An analysis was made of 200 cases of herpes simplex encephalitis from the French, American, and English literature (references available on request). Twenty-five of these cases were treated with idoxuridine and 17 cases were
Table 1. Summary of cases of herpes simplex encephalitis treated with idoxuridine

| Author            | Age & Sex | Duration of disease at start of treatment (days) | Total dose of idoxuridine (g) and route | Course and Outcome       |
|-------------------|-----------|-----------------------------------------------|----------------------------------------|--------------------------|
| Breeden et al.    | 34 M      | 22                                            | 39 g i.v.                              | Improved; recovered      |
| (1966)            |           |                                               |                                        |                          |
| Evans et al.      | 8 F       | 55                                            | 7.5 g i.v.                             | Improved; recovered; handi-capped |
| (1967)            |           |                                               |                                        |                          |
| Marshall          | 13 M      | 15                                            | 7-5 g i.v.                             | Improved; recovered      |
| (1967)            |           |                                               |                                        |                          |
| Buckley and       | 41 F      | 11                                            | 1 g intracarotid                       | Improved; recovered      |
| MacCallum (1967)  |           |                                               |                                        |                          |
| Bellanti et al.   | 11 F mths | 14                                            | 1.92 g i.v.                            | Improved; recovered      |
| (1968)            |           |                                               |                                        |                          |
| Rappel and        | 58 M      | 16                                            | 500 mg/kg i.v.                         | Improved; died           |
| Brihaye (1969)    | 45 M      | 19                                            | 4 g i.v.                               | Died                     |
|                   | 56 M      | 27                                            | 500 mg/kg i.v.                         | Improved                 |
|                   | 12 F      | 16                                            | 320 mg/kg i.v.                         | Recovered                |
|                   | 65 F      | 9                                             | 500 mg/kg i.v.                         | Improved; died           |
|                   | 45 F      | 18                                            | 500 mg/kg i.v.                         | Improved; died           |
| Duffy (1969)      | 43 M mths | 10                                            | 400 mg/kg i.v.                         | Improved; recovered      |
|                   | 4 mths    |                                               | Similar dosage                         | Improved                 |
| Dayan and Lewis   | 60 M      | 30 g s.v.e.                                   |                                        | No change; died          |
| (1969)            |           |                                               |                                        |                          |
| Golden et al.     | 10 days   | 8                                             | 500 mg/kg i.v.                         | Improved; recovered; im- paired |
| (1969)            |           |                                               |                                        |                          |
| Goldman et al.    | 20 M      | 12                                            | 13.5 g i.v.                            | Improved; recovered      |
| (1970)            |           |                                               |                                        |                          |
| Meyer et al.      | 57 F      | 13                                            | 24 g i.v.                              | No change; died          |
| (1970)            | 24 F      | 13                                            | 30 g i.v.                              | Recovered                |
|                   | 22 F      | 14                                            | 30 g i.v.                              | Recovered                |
|                   | 10 M      | 8                                             | 15 g i.v.                              | Recovered                |
|                   | 16 F      | 3                                             | 30 g i.v.                              | Recovered                |
|                   | 62 F      | 6                                             | 6 g i.v.                               | Died                     |
| Silk and Roome    | 6 M       | 8                                             | 11.5 g i.v.                            | Improved; recovered; handi-capped |
| (1970)            |           |                                               |                                        |                          |
| Charnock and      | 19 F days | 15                                            | 410 mg/kg i.v.                         | Improved; recovered      |
| Cramblett (1970)  |           |                                               |                                        |                          |
| Illis and Merry   | 39 M      | 21                                            | 15 g i.v.                              | Improved; recovered; handi-capped |
| (1970)            |           |                                               |                                        |                          |
|                   | 57 M      | 42                                            | 12 g i.v.                              | Improved; recovered; handi-capped |
|                   | 71 F      | 30                                            | ?                                      | No change; died          |
|                   | 26 F      | 8                                             | 21 g i.v.                              | Improved; died           |
Table 2. Summary of cases of herpes simplex encephalitis treated with ACTH or steroids

| Author                        | Age & Sex | Duration of disease at start of treatment (days) | Method of treatment | Course and Outcome                                      |
|-------------------------------|-----------|--------------------------------------------------|---------------------|--------------------------------------------------------|
| Illis and Merry               | 58 M      | 21                                               | ACTH 40 u/day       | Improved; recovered                                    |
|                               | 58 M      | 17                                               | Cortisone 75 mg/day | No change; died                                        |
|                               | 63 F      | 29                                               | Hydrocortisone 300 mg/day | No change; died                                      |
|                               | 77 M      |                                                  | Prednisone          | Deteriorated; improving 3 months after onset          |
|                               | 26 F      |                                                  | ACTH just before onset and continued ACTH 60 u/day | No change. Later slight improvement IDU; died          |
|                               | 28 F      | 36                                               | Dexamethasone 16 mg/day | Improved; recovered                                   |
| Evans et al. (1967)           | 8 F       | 6                                                | Hydrocortisone and ACTH | No change; improved after IDU |
| Upton et al. (1971)           | 20 F      | 7                                                | Dexamethasone 20 mg/day | Improved; recovered                                   |
| Blackwood et al. (1966)       | 20 M      | ?                                                | ACTH                | Possible improvement; died                            |
| Blackwood et al. (1966)       | 13 F      | ?                                                | ACTH                | No change; died                                        |
| Carmon et al. (1965)          | 35 F      | 10                                               | i.m. Hydrocortisone | Improved; recovered                                   |
| Carmon et al. (1965)          | 70 F      | ?30                                              | Hydrocortisone      | Gradually improved; recovered                         |
| Leider et al. (1965)          | 5 F       | 9                                                | “Steroids”          | Improved; died                                        |
| MacCallum et al. (1964)       | 61 F      | 10                                               | Hydrocortisone 400 mg/day | No change; died                                      |
| McKee et al. (1968)           | 17 F      | ?                                                | Steroids            | No change; died                                        |
| Page et al. (1967)            | 25 M      | 10                                               | Dexamethasone 16 mg/day | No change; died                                      |
| Page et al. (1967)            | 30 F      | ?                                                | Dexamethasone 16 mg/day | No change; died                                      |
| Raychoudhury and Seidel (1968)| 14 M      | 35                                               | ACTH 80 units daily | Slowly improved; recovered                            |
| Ross and Stevenson (1961)     | 14 M      | ?                                                | Cortisone           | Improved; recovered                                   |
| Ross and Stevenson (1961)     | mths      | 28 F                                             | Cortisone           | Slow improvement over next 4 months; recovered. Severe deficit |
| Silk and Roome (1970)          | 6 M       |                                                  | Prednisolone 40/day | No response; subsequent improvement on IDU            |
Table 3. Age and sex incidence, herpes simplex encephalitis

| Age   | Total | Female | Male |
|-------|-------|--------|------|
| 0-10  | 47    | 17     | 30   |
| 11-20 | 17    | 10     | 7    |
| 21-30 | 32    | 9      | 23   |
| 31-40 | 16    | 4      | 12   |
| 41-50 | 21    | 11     | 10   |
| 51-60 | 22    | 9      | 13   |
| 61-70 | 12    | 6      | 6    |
| 71-80 | 6     | 3      | 3    |
| Totals| 173   | 69     | 104  |

Table 4. Mortality rate of untreated cases by decade

| Age   | Mortality rate (%) |
|-------|--------------------|
| 0-10  | 68                 |
| 11-20 | 56                 |
| 21-30 | 83                 |
| 31-40 | 50                 |
| 41-50 | 70                 |
| 51-60 | 77                 |
| 61-70 | 75                 |
| 71-80 | 83                 |

treated with ACTH or steroids. In addition, 10 cases of herpes simplex encephalitis were treated at this Centre (4 with idoxuridine, and 6 with steroids or ACTH). The cases from the literature and personal cases were pooled for the purpose of this study. The treated cases are listed in Tables 1 and 2.

RESULTS
The age and sex incidence of 173 cases of herpes simplex encephalitis extracted from the literature is given in Table 3 and it is noteworthy that the majority of cases (47) were in the first decade, and of these 24 were under one year old.

For the 174 cases who were not treated with idoxuridine, the mortality rate was 70 per cent. The percentage death rates by decade are given in Table 4.

The information regarding treatment with ACTH or steroids is almost certainly incomplete and only 17 cases definitely treated with these drugs.
were found in the literature. These cases, together with 5 personal cases, make a total of 23 patients. The mortality rate in these cases was 44 per cent. In addition two cases with no response on steroids showed subsequent improvement when treated with idoxuridine (see Table 2).

Twenty-five cases treated with idoxuridine were adequately documented in the literature, and these, with 4 personal cases, are listed in Table 1. Mortality rate in the 29 cases treated with idoxuridine is 31 per cent. Toxic effects of idoxuridine treatment were common (Table 5) but nearly always transient and reversible. The commonest toxic effects were leucopenia and thrombocytopenia, stomatitis and glossitis, and alopecia. No deaths were definitely attributable to the effects of idoxuridine.

**Table 5. Summary of toxic effects of idoxuridine treatment in herpes simplex encephalitis. 19 of 29 patients treated had some toxic effects.**

| Toxic effects                                    | No. of patients |
|-------------------------------------------------|-----------------|
| Bone marrow depression (anaemia, leucopenia, thrombocytopenia) | 16              |
| Abnormal liver function tests                   | 10              |
| Alopecia                                        | 8               |
| Stomatitis and glossitis                        | 5               |
| Gastro-intestinal haemorrhage                   | 1               |
| Diarrhoea                                       | 1               |
| Jaundice                                        | 2               |

**DISCUSSION**

*Steroids and ACTH*

The use of ACTH and corticosteroids in the treatment of severe infection remains to some extent controversial. In the case of bacterial infections, results have been investigated repeatedly and a certain amount of scepticism remains. In viral infections, evaluation has been even more difficult partly because of the frequent publication of isolated cases with favourable results in a hopeless situation and partly because individual physicians treat too few cases to allow a personal assessment of therapy. Steroids *in vitro* enhance virus replication (Kilbourne and Horsfall, 1951) and suppress the synthesis and action of interferon (Kilbourne et al., 1961). Intraperitoneal injection of poliovirus in animals treated with steroids produces paralysis, but no paralysis is produced if the injection is into animals not treated with steroids (Schwartzman, 1954). The local application of steroids to patients with herpes zoster and
herpes simplex infections may result in severe exacerbation. On the other hand, many of the ill effects of virus encephalitis may be due to inflammatory changes rather than cell destruction due to virus replication, and in this situation the administration of steroids may be indicated.

Tokumaru (1968) inoculated guinea-pigs intracerebrally with herpes simplex virus and observed the effect on survival of various treatments. Both idoxuridine and interferon (each given for five days) showed a therapeutic effect. Hydrocortisone had no effect given as a five-day course or as a single dose. These results are, of course, not strictly applicable to man, since the animals were infected by a sudden massive single large dose of virus and this almost certainly does not occur in human infection.

The use of steroids in the treatment of encephalitis is, therefore, still controversial and there is much evidence suggesting that such treatment may be positively harmful. Webb (1969) points out that it is justifiable to give steroids in large doses for a short time at the onset of the encephalitic stage of the illness. Steroids are then most likely to produce benefit by reducing oedema, and at this time blood and CNS interferon should both have been produced. That is, steroids must be given after the stage of viraemia and when antibodies are present. Unfortunately, in some cases of herpes simplex encephalitis death occurs before there is much antibody and the real damage in acute encephalitis may well be done before antibody formation.

Bøe et al. (1965) described a retrospective study (in Norway) of the effect of corticosteroid treatment in 346 patients with acute meningo-encephalitis. Of these, 91 cases had post-infectious meningo-encephalitis, 153 were not post-infectious, and 102 had encephalitis of uncertain type. In all three groups the mortality rates were higher in the treated group (50 to 22 per cent; 30 to 19.5 per cent; 53.3 to 26.4 per cent respectively). During the acute stage of the illness 106 cases were comatose. In this group, cases more likely to receive steroids, the results indicated a higher mortality rate in the treated (69.2 per cent) than in the non-treated group (58.2 per cent). The frequency of neurological sequelae was also higher in the treated group (73 to 27.6 per cent).

Page et al. (1967), reporting two cases who were treated with dexamethasone and died, felt that steroids were contra-indicated in this condition. However, Upton et al. (1971) recorded two cases of herpes simplex encephalitis who improved with dexamethasone. They concluded that steroids should be used as an emergency treatment in this condition, and suggested that the high mortality rate is partly due to the use of idoxuridine with its known toxic effects. However, they ignored the fact that the mortality of untreated cases is much higher and that all adverse effects have been transient and reversible.
Longson and Beswick (1971) contested the conclusions of Upton et al. and pointed out that steroids may inhibit the production of interferon, and of viral antibodies, increase viral virulence and, particularly in herpes simplex infections, lead to a worsening of the disease with occasionally disastrous results. However, these adverse effects take a long time to develop and the valuable anti-inflammatory effect of steroid therapy can be achieved in a few days, long before any damage is done to the patient's mechanisms of resistance to infection. Indeed, disasters associated with H. hominis and H. varicellae in steroid-treated patients have mostly occurred in patients already having prolonged steroid therapy who have then become infected with one of these viruses.

In this report, analysis of cases of herpes simplex encephalitis treated with ACTH and steroids shows that the mortality rate may be lowered from 70 to 44 per cent. There is no evidence that the quality of survival is affected by the use of steroids or ACTH. It is noteworthy that two cases treated with these drugs showed no improvement but subsequently recovered after treatment with idoxuridine.

**Cytarabine**

Cytarabine is effective against DNA viruses in cell culture and is probably as active as idoxuridine in the treatment of herpetic keratitis. Juel-Jensen (1970) reported a case of a 22-year-old male who developed a severe herpes simplex infection with fever, malaise, lymphadenopathy, headache, and clouding of consciousness. The herpes titre rose from 1:4 to 1:128 in 12 days. Treatment with cytarabine 0.3 mg/kg daily intravenously was started 2 days after the onset and was carried on for 5 days. Improvement started within 12 hours and continued. The patient was discharged from hospital about 10 days after the onset of the illness. No toxic effects occurred on treatment.

**Idoxuridine**

Idoxuridine is a thymidine analogue which differs from thymidine in having an iodine atom replacing the 4-methyl group. Idoxuridine inhibits virus replication by competitively blocking the uptake of thymidine into the DNA molecule. Idoxuridine itself becomes incorporated in the place of thymidine and the DNA molecule thus formed is aberrant. The earliest clinical use of systemic idoxuridine was in the treatment of neoplastic disease. It was noticed that patients treated with idoxuridine did not develop positive smallpox vaccination and this led to the suggestion that idoxuridine might be useful in the treatment of systemic DNA-viral infections.

Intravenous infusion of idoxuridine at a dosage of 100 to 120 mg/kg/
bodyweight over a period of 2 to 3 hours daily for 5 to 6 days shows that significant blood levels of idoxuridine are maintained for approximately 4 hours. At this sort of dosage toxic effects include leucopenia, thrombocytopenia, stomatitis, and alopecia, and these effects are related to the capacity of idoxuridine to inhibit rapidly dividing and proliferating cells (Calabresi, 1963). The urinary excretion of idoxuridine is rapid and about half the dose is likely to be excreted within 13 hours. Breeden et al. (1966) administered radioactive idoxuridine intravenously in a case of necrotising temporal lobe encephalitis due to herpes simplex to see whether there was any uptake of the drug into the brain. A brain scan failed to show uptake. This could have been due to inadequate drug concentration or failure of the radioactive idoxuridine to enter the brain. Experimental distributions of radioactive labelled idoxuridine in plasma and CSF of dogs have shown a CSF:plasma radioactivity ratio of 0.1:1. There was no evidence of any significant quantity of idoxuridine reaching the CSF after intravenous injection. Even when idoxuridine is given directly into the CSF there is a rapid disappearance of the drug, with concomitant appearance of iodouracil and iodine suggesting that there is a rapid metabolism (Clarkson et al., 1967). Buckley and MacCallum (1967) measured the lumbar CSF levels of idoxuridine two hours after intra-arterial administration in a patient with herpes simplex encephalitis. Less than 20 pg/ml was present. Intrathecal idoxuridine in rabbits infected with herpes simplex produced no beneficial effect.

Although idoxuridine has been very effective in the treatment of corneal herpes simplex infections, its efficiency in treating systemic viral infections has not previously been adequately established. Indeed, from the data it would seem that idoxuridine is too rapidly metabolised when injected intravenously or into the cerebrospinal fluid to have any real effect in encephalitis. However, there is no definite reason why a drug’s effectiveness should be equated with the level it attains in the cerebrospinal fluid and there have been many reports of cases in which idoxuridine treatment has seemed to be of benefit. The analysis and comparison of the mortality rates of untreated cases with those of idoxuridine treated cases indicates the potential usefulness of idoxuridine. The mortality rate, using idoxuridine, falls from 70 to 31 per cent. Many of the treated cases, although they recovered, were unfortunately left with grave neurological or mental sequelae. The clinical impression is that the earlier that patients are treated, the better the chance of survival, but an analysis of the reported cases (Table 6) indicates that even in cases treated several weeks after the onset of the illness there is a good chance of survival. The residual neurological defects, however, are probably more severe in the late treated cases.
Table 6. Relationship of time of starting treatment to death or recovery

| Time from onset of treatment (days) | Death | Recovery |
|-----------------------------------|-------|----------|
| 0–7                               | 1     | 1        |
| 8–14                              | 2     | 9        |
| 15–21                             | 2     | 5        |
| 22–28                             | 0     | 2        |
| 29–35                             | 0     | 0        |
| 36–42                             | 0     | 1        |
| 43–49                             | 0     | 0        |
| 50–56                             | 0     | 1        |

Table 7. Relationship of age of patient to death or recovery in treated cases.

| Age (years) | Deaths | Recovered |
|-------------|--------|-----------|
| 0–1         | 0      | 4         |
| 1–10        | 0      | 3         |
| 11–20       | 0      | 4         |
| 21–30       | 0      | 2         |
| 31–40       | 0      | 3         |
| 41–50       | 1      | 3         |
| 51–60       | 3      | 2         |
| 61–70       | 2      | 0         |

The treated patients who died tended to be older than those who survived following treatment (Table 7) but the numbers are too small to permit any firm conclusion to be drawn. However, the mortality rate by decade of untreated patients (Table 4) indicates that the mortality varies little with age and there remains a strong impression that the chances of idoxuridine treatment being of benefit is greater in patients under the age of 50.

Decompression

In 1956, Dodge and Cure reported the first case in which the diagnosis of encephalitis with inclusion bodies was established during life by brain biopsy. Serial neurological studies, although not conclusive, suggested that the causal agent was herpes simplex virus. The case was unusual in that the patient survived the acute illness. The authors considered that survival during the acute phase was at least partly due to surgical decompression carried out on the 5th day after onset at a time when there was clinical and
radiological evidence of raised intracranial pressure. Since that time several authors have drawn attention to the possible value of decompressive craniotomy in cases where there is evidence of raised intracranial pressure and progressive clinical deterioration (Drachman and Adams, 1962; Martins et al., 1964; Pierce et al., 1964; Carmon et al., 1965; Adams and Jennett, 1967; Marshall, 1967; May et al., 1967; Page et al., 1967). The mortality rate of the patients reported by these authors is 30 per cent, and this figure is considerably lower than the overall mortality of untreated cases. The figures are, of course, not strictly comparable since the cases selected for decompression were characterised by a progressive deterioration and evidence of raised intracranial pressure. Furthermore, some of the cases had treatment with idoxuridine as well as decompression. Nevertheless, it would appear that decompressive craniotomy is of value in selected cases.

**SUMMARY AND CONCLUSION**

Analysis of the literature on herpes simplex encephalitis indicates that the overall mortality rate of untreated cases is 70 per cent. From the literature and from personal cases it appears that the mortality rate when cases are treated with ACTH and steroids falls to 44 per cent. However, at least two cases have been reported in which treatment with ACTH and steroids had no effect but subsequent recovery occurred after treatment with idoxuridine. Analysis of cases treated with idoxuridine shows that the mortality falls to 31 per cent. Adverse effects are common but transient and there is no evidence that death can be attributed to the toxic effects of idoxuridine. There is a strong clinical impression that the earlier patients are treated with idoxuridine the better the chance of survival. However, the survival rate was good even in those cases treated several weeks after the onset of the illness. The residual neurological defects are probably more severe in the later treated cases. Decompression is a useful adjunct to treatment in appropriate cases. The treatment of choice in herpes simplex encephalitis is idoxuridine.

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