Withdrawal of parenteral phenobarbitone – implications for resource-poor countries

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Parenteral phenobarbitone is an integral part of the management of status epilepticus, especially in the context of resource-poor countries. It is highly effective at controlling seizures. It is safe, cheap, can be given by rapid intravenous push or intramuscular route, boluses can be repeated, and it is recommended as part of the Advanced Paediatric Life Support guidelines. The proposed alternatives lack efficacy, practicality and/or place the child in status epilepticus at risk of respiratory compromise. The impact of the loss of parenteral phenobarbitone would be increased cardiac complications, lack of early seizure control, prolonged seizures resulting in brain damage and systemic complications. Increased numbers of patients will require artificial ventilation in centres without facilities, and centres with facilities will be unable to cope with the load of ventilated patients because of lack of safe transport systems and bed space.

S Afr Med J 2005; **95**: 422-423.

Status epilepticus in childhood is a common medical emergency requiring swift and effective termination in order to limit subsequent adverse complications. Parenteral phenobarbitone is the main agent used in most centres to attain this.

The production of parenteral phenobarbitone in South Africa stopped in December 2004; this was a worldwide policy by the suppliers.

Phenobarbitone is recommended in the most recent Advanced Paediatric Life Support (APLS) guidelines (Fig. 1).[1] Its withdrawal has even more serious repercussions for the management of status epilepticus in resource-poor countries (RPCs).

Phenobarbitone can be administered by slow intravenous push or intramuscularly, a route that is often used in RPCs.[2,3] It is an effective agent for the control of status epilepticus.[4,5] Side-effects are respiratory depression and lowering of blood pressure, the underlying disease being the main related factor and the rate of rise of serum levels.[6] Accordingly it can be and is used at all levels of hospital care. The authors concur with the APLS guidelines and have recommended the use of phenobarbitone for the third line of treatment for the management of status epilepticus in RPCs (Fig. 2).[7,8]

If the supply of parenteral phenobarbitone terminates, the alternatives for our setting are limited. Lorazepam or other benzodiazepines are associated with increased risk of respiratory depression[9] and the risk will increase where benzodiazepines are already used as first-line treatment.

Phenytoin is the alternative agent to phenobarbitone in the APLS algorithm. Intravenous phenytoin is associated with fatal haemodynamic complications, serious skin reactions at the injection site and cardiac arrhythmias.[10] The agent should be administered into a large vein (but ideally not central), via a slow infusion over 30 minutes through a syringe driver. The child should have cardiac monitoring. These facilities for safe administration are often not available in hospitals in RPCs. Following the guidelines, the administration of phenytoin takes three times as long as the slow push of phenobarbitone. The delayed time to administer therapy may increase the risk of refractory status epilepticus, which is associated with subsequent brain damage.[11] Furthermore, the APLS guidelines recommend measuring levels 60 - 90 minutes after completion of the infusion, but this is only available in a few tertiary or research centres in RPCs. Although more economical than the newer anticonvulsants, parenteral phenytoin is still four times the cost of phenobarbitone. In addition, it is not as fast or effective at controlling status epilepticus as phenobarbitone.[4,5,12,13]

In conclusion, although pharmaceutical companies may not make substantial profits from the manufacture of phenobarbitone, withdrawal of this drug is likely to have a devastating effect on the outcome of status epilepticus in RPCs. Currently various bodies are attempting to ensure that this agent remains available in South Africa. This crisis should be viewed as an example of the potential dependency of the medical profession on drug company policy, and the latter's potentially catastrophic effects on the care of our patients.

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Airway

High-flow oxygen

Don't ever forget glucose

Vascular access ?

Yes → No

Lorazepam
0.1 mg/kg IV/IO

Diazepam (rectal)
0.5 mg/kg OR
Midazolam (buccal)
0.5 mg/kg

Lorazepam ← YES ← Vascular access?
0.1 mg/kg IV/IO

NO

Paraldehyde 0.4 ml/kg PR

i.e. 0.8 ml/kg of prepared solution

Phenytoin 18 mg/kg IV/IO over 30 minutes

Or if already on phenytoin give phenobarbitone

20 mg/kg IV/IO over 10 minutes

Rapid sequence induction with thiopental sodium (thiopentone) 4
mg/kg IV/IO

Fig. 1. APLS status epilepticus algorithm (2005)[1] (IV = intravenous; IO = intra-osseous; PR = per rectum).

PR diazepam (0.5 mg/kg)

IV access IV diazepam (0.3 mg/kg)
(take bloods for glucose, gas, electrolytes,
full blood count and culture)

Access failure/delay – gain IO access or
intranasal midazolam 200 µg/kg

IV phenobarbitone (20 mg/kg)

Repeat phenobarbitone (10 mg/kg)

Repeat phenobarbitone (10 mg/kg)

Refer to PICU for intubation and sodium pentothal
infusion

Alternatives: (*i*) lorazepam (0.1 mg/kg), a faster-acting alternative to diazepam for bolus IV intervention; (*ii*) midazolam intranasally (200 µg/kg) or sublingually (500 µg/kg) if there is no venous access; (*iii*) midazolam infusion loading at 200 µg/kg by slow IV injection, then titrating an infusion between 30 µg/kg/h and 300 µg/kg/h – alternatively, clonazepam (Rivotril) infusion if seizure control is not gained after the first phenobarbitone infusion; (*iv*) phenytoin (20 mg/kg over 20 minutes) if there is known adverse reaction to phenobarbitone (monitor for cardiac arrhythmias); (*v*) watch carefully for drug-related respiratory depression; and (*vi*) intubation, ventilation and administration of sodium pentothal infusion should only be performed in a centre with trained anaesthetic and paediatric intensive care.

PR = per rectum; IV access = if IV access available; IO = intra-osseous; PICU = paediatric intensive care unit; ABCD = airway, breathing, circulation, drugs.

Fig. 2. Management of status epilepticus in South Africa[8] – ABCD (oxygen, monitor saturation, pulse and blood pressure, glucose).

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Demographics and presenting clinical features of childhood systemic lupus erythematosus

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Objectives. To review the presentation and characteristics of children with systemic lupus erythematosus (SLE).

Methods. The records of children with sufficient American College of Rheumatology (ACR) criteria for SLE treated by the renal units of the Johannesburg and Chris Hani Baragwanath hospitals, and the arthritis clinic of the Johannesburg Hospital between January 1974 and March 2000 were reviewed. The clinical presentation, age distribution and race were examined.

Results. A total of 36 children met the criteria. There were 26 girls and 10 boys, with a mean age of 11.5 and 10.2 years respectively. The male-to-female ratio was 1:2.6 overall, with a ratio of 1:1.2 under 10 years and 1:4 over 10 years. There were

15 white, 2 Indian and 5 coloured patients. The 14 black patients all presented after 1986. Rashes were found to be the commonest clinical feature present at the time of diagnosis, followed by polyarthritis and renal pathology. Constitutional symptoms were common, as were generalised lymphadenopathy and hepatosplenomegaly, while neurological, pulmonary and cardiac signs and symptoms were less common. Renal disease was present in 58% of patients on presentation.

Conclusion. There is a diverse array of presenting features in childhood SLE. There has been increased recognition of the disease in young black South Africans since 1986.

S Afr Med J 2005; 95: 424-427.

Systemic lupus erythematosus (SLE) is a multisystem, autoimmune disorder characterised by the formation of antibodies to cellular components.

Worldwide, 15 - 17% of SLE patients present before 16 years of age, with a peak incidence at 10 - 14 years. It is rare in children below 4 years old, and there is a female predominance in adolescence and adulthood. The true incidence of childhood SLE is difficult to determine. Old data suggest that it was a very rare disease, but this was largely because mild and early cases went unrecognised until end-organ damage made the disease unmistakable. Even today, many children present late as the early signs are not recognised and linked with this disease.[1]

Children may present with skin rashes, arthritis, and nonspecific constitutional symptoms that may precede the finding of organ-specific disease. The incidence of renal pathology is high both on presentation and later in the disease process. It has also been suggested that race plays a role in SLE, predominantly in the outcome. In South Africa SLE was thought to be rare in black patients. In total there have been only 4 publications dealing with childhood SLE in South Africa between 1981 and 1994. As there is a paucity of data in South Africa on childhood SLE, this study aimed to document the

clinical features and demographics of children with SLE at specific referral centres in Gauteng.

Patients and methods

A retrospective review and analysis was done of all the children attending the renal and arthritis clinics at Johannesburg Hospital and the renal clinic at Chris Hani Baragwanath Hospital from January 1974 to March 2000. These are academic teaching hospitals and referral centres of the University of the Witwatersrand. These referrals were from primary care paediatricians, secondary-level hospitals, and the hospitals' general wards, which accept patients from Gauteng and North-West provinces. A single reviewer (GF) examined all the records. Patients who fulfilled 4 or more of the American College of Rheumatology (ACR) criteria for SLE, either on presentation or sequentially, were included.[2] Gender, race, age and clinical features on first presentation were recorded. The patient's age was recorded at the time of initial presentation at the referring centre. Clinical features documented in referral letters or obtained at the time of the first visit were also recorded. The results of renal biopsies done within the first 3 months were included as part of the initial presentation.

Results

Thirty-six patients fulfilled the ACR criteria. There were 10 boys and 26 girls, reflecting a ratio of 1:2.6 overall, with a ratio of 1:1.2 under and 1:4 over 10 years. The mean age on presentation was 10.9 years (boys 10.2 years, girls 11.3 years), with a range of 4.8 - 16.1 years. There were 15 white, 14 black, 2 Indian and 5 coloured patients. All the black patients presented after 1986.

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Clinical features

Cutaneous signs were the commonest feature on initial presentation (Table I). Twenty-eight patients had 1 or more of the typical lupus rashes (77%), with 47.2 % having a malar rash, and 25% having mucocutaneous ulceration. Constitutional features were common, but nonspecific. Hepatosplenomegaly, generalised lymphadenopathy, arthritis and arthralgia were also common as were central nervous system (CNS) complaints, including persistent headaches, always a difficult symptom in childhood.

Table I. Clinical presenting features

Features	Number	Percentage
Cutaneous features (malar rash 17, discoid lesions 4, vasculitis 8, alopecia 5, mucocutaneous ulceration 9, photosensitivity 4, urticaria 1)	28	77
Constitutional features (fever, myalgia, fatigue, weakness, weight loss)	20	55.5
Renal disease (nephrotic syndrome 8, hypertension 3, acute glomerulo-nephritis 3, haematuria 1, renal failure 1)	16	44.4
Arthritis	14	38.8
Lymphadenopathy	12	33.3
Hepatosplenomegaly	8	22.2
Serositis (pericardial effusion 3, pleural effusion 4)	7	19.4
CNS symptoms (seizures 1, encephalopathy 1, depression 2, hemiparesis 1, chorea 1, headache 3, psychosis 1)	7	19
Arthralgia	4	11.1
Abdominal pain	4	11.1
Pneumonia	3	8.3
Raynaud's phenomenon	3	8.3
Cardiac disease	3	8.3
Disseminated sepsis	2	5.5
Pancreatitis	1	2.7
ITP	1	2.7

ITP = idiopathic thrombocytopenic purpura.

Three patients presented with pneumonia and 3 had Raynaud's phenomenon. There were 3 patients with cardiac disease (cardiomyopathy, cardiac failure, myocarditis), 2 with disseminated sepsis and 4 with abdominal pain, 1 of which cases proved to be pancreatitis. One patient (a boy) was treated for 2 years for idiopathic thrombocytopenic purpura (ITP).

The duration from onset of symptoms to diagnosis was not always known. This information was available for 20 of the 36 patients (55.5%). The average time to diagnosis for these 20 patients was 16 months from onset of symptoms. In those children without arthritis and cutaneous manifestations, it took longer for the diagnosis to be established, and it was made most quickly in those presenting with renal disease, indicating that a higher index of suspicion existed in these patients. The longest recorded duration of 5 years was in a girl who had a hemiparesis and primarily neurological symptoms since the age of 7. She had been followed up for these symptoms, and the diagnosis was made at 12 years old when she developed cutaneous features (discoid lesions and mucocutaneous ulceration).

Renal disease

Twenty-one patients had early renal biopsies, 16 of whom presented with symptoms of disease. On biopsy 3 of these patients were found to be of mixed World Health Organization (WHO) classification, and were then classified under the dominant class. Sixteen of the patients were either class III or IV at presentation (76% of the total biopsied). Presentation of the children with renal disease was varied; nephrotic syndrome was the most common. One child was in renal failure at the time of diagnosis.

Discussion

This is the first series on South African children with SLE. A review of the literature revealed 4 reports of children with SLE in South Africa, a report of 3 cases in 1981,[3] and a report in 1986[4] on 6 cases of SLE with lupus nephritis. The first case report of a black child with this disease was published in 1991,[5] although there were undoubtedly patients recognised before this time. A subsequent report in 1994 dealt with outcomes.[6]

The racial characteristics are interesting in a country like South Africa. The group consisted of 42% white patients, which is not representative of the demographics of the country. Some of this may be explained on a historical basis where under the apartheid system black patients had less access to tertiary-level health care. SLE was thought to be extremely rare in this group and a large number of patients may have gone undiagnosed, or may have died with the disease unrecognised. The prevalence of SLE in adult black South Africans has been estimated to be 12.2/100 000,[7] but no figures exist for children in South Africa. A 'best guess' estimate of the prevalence in our area is 1/100 000, extrapolated from the data provided by Ransome and Thomson.[4,8] The number of black patients presenting after 1986 shows that SLE is increasingly recognised in this group of patients in South Africa.

This series showed the age of presentation, with a peak at 10.9 years and no patient presenting under the age of 4. However, the mean age is lower than in other reported series,[9] which have suggested a peak in the adolescent years. Before about 1995, in the hospitals from which this study population

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was drawn, all children over the age of 12 were considered better managed in the adult wards and clinics because of severe lack of bed space. To some degree this may explain the relative paucity of teenagers, especially boys, in this group. The male/female ratio in childhood has varied in reported studies from 1:5.5 (Boston) and 1:2.8 (Israel) to the same rate as in adults (1:20, UK).[10] In this series our ratio was 1:2.6 (72% female); in children under 10 years the male/female ratio was almost equal (1:1.2) while in those 10 years and older it was 1:4.

Among the most prominent presenting features of childhood SLE are arthralgia, arthritis, malar rash and fever, which were well demonstrated here. The classic malar rash present in 47% of patients in this study has been described as occurring in about one-third of patients. Possibly this was so common in our group as it is an obvious lupus symptom at the time of referral. More commonly, patients have been reported to have maculopapular rashes in sun-exposed areas (SLE being typically very photosensitive), mucocutaneous ulceration and vasculitis of the fingers that may be associated with Raynaud's phenomenon, a common phenomenon in adolescent girls. Fourteen of these children had arthritis at presentation. The arthritis of childhood SLE, as of adults, is generally non-destructive and non-deforming. The commonly affected joints are the knees, wrists, and proximal interphalangeal joints. It may be migratory. In this study this incidence was high at 38.8%, with a further 11% reporting arthralgia. If combined with other musculoskeletal symptoms such as myalgia and weakness, the percentage rises even higher.

Nephritis, often with a nephrotic component, is not unusual as the presenting feature of SLE, as the kidney is the most commonly affected organ in children. Fifty-eight per cent of our patients had evidence of lupus nephritis on biopsy at the time of presentation. Prevalence rates in childhood range from 50% to 80% of all patients.[11] Outcomes are dependent on the severity of the histopathological lesions. In this study, 76% of the total number of children biopsied (21) were WHO class III or IV, indicating a poorer prognosis. In several instances children have presented with 'full house' nephropathy before the onset or recognition of SLE.[12]

There were several unusual presentations such as cardiac diseases usually associated with longer time of disease, pancreatitis, and disseminated sepsis as the first presentation. The children who presented with these diseases had an average time of 8 months to diagnosis from first presentation, but the actual duration of symptoms is somewhat uncertain.

Cardiac disease may present as myocarditis, pericarditis, pericardial effusion, cardiac tamponade, and endocarditis (Libman-Sacks type). It is interesting that 3 patients (8.3%) had cardiac disease as their presenting feature in this study. While this has been described previously, it suggests that lupus not only presents late in our population, but may also have an

insidious course until end-organ disease is present.

Documentation of pancreatitis in paediatric SLE is uncommon. Severe SLE may be complicated by both acute and chronic pancreatitis, and pancreatic pseudocyst formation has been reported, although this is an extremely rare situation.[13]

Disseminated sepsis is a manifestation of the immune suppression in SLE. The most common sites for infection are the skin, respiratory tract, urinary tract and CNS although the osteoarticular system is also frequently involved. As these systems are involved on the basis of primary immune suppression, it is not surprising that some of the children in this series initially presented with symptoms of sepsis.[14]

In our series 19% of patients had 1 or more neurological symptoms on presentation. CNS involvement includes frank psychosis, strokes, seizures, chorea and coma. The patients in this series showed the presence of all of these, which frequently occur without warning during the progression of the disease, but may be presenting features, as was the case here. Children have presented for neurological or psychiatric assessment before the diagnosis of SLE, and in 1 series of 10 patients, all had symptoms within 4 years of diagnosis including neurological and psychiatric symptoms.[15] It is interesting that the child in this series with the longest history before her diagnosis was made, was being treated for a variety of neurological complaints. Most commonly reported is the occurrence of seizures, followed by headaches, but our series showed headaches as the commonest complaint on presentation, followed by depression. Psychosis and depression are both known to be presenting features. The pathogenesis of neuropsychiatric SLE is probably multifactorial. It may result from cerebritis, vasculitis, or hypertension; it may also be the result of therapy, or secondary to events such as cerebrovascular accidents. In adolescence, interpreting these signs may be made more difficult by the psychological problems associated with coping with a chronic illness.[1]

Pulmonary features occuring in children with lupus include pleuritis, acute pneumonitis, chronic interstitial lung disease, pulmonary fibrosis, alveolar haemorrhage, respiratory and diaphragm myopathy, and pulmonary hypertension. Studies have reported incidences from 5% to 67%. Children may also not have symptoms of pulmonary disease but show significant impairment on lung function testing.[16] In this study there was only documentation relating to acute pneumonitis on presentation. No references were found to pulmonary function testing at diagnosis. We are therefore unable to judge the real incidence of early pulmonary disease in our group of patients.

One patient presented with ITP, which was treated for some time before the diagnosis was made. Such a patient may have had no other signs at the time of initial presentation, but careful periodic re-evaluation will reveal the progression to SLE.

Table II. Warning signs of childhood SLE

A. Consider if 2 or more of the following are present, especially if there is single-organ involvement of any feature mentioned under B:

1. Unexplained rash
2. Photosensitivity
3. Raynaud's phenomenon
4. Oral ulcers
5. Arthritis/arthralgia
6. Serositis
7. Ongoing constitutional symptoms
8. Lymphadenopathy/hepatosplenomegaly

B. SLE is highly likely if there is multiorgan involvement of 2 or more of the following, and any feature mentioned under A:

1. Renal disease with proteinuria/haematuria
2. Neurological disorder
3. Haematological disorder
4. Cardiac/pulmonary/GIT symptoms

GIT = gastrointestinal tract.

In summary, this study documents the diverse ways in which children with SLE in South Africa have presented, and the incidence of renal disease in our population. The findings suggest that patients in our population are being missed early on, and therefore present late, and that childhood SLE is an insidious disease initially. Table II summarises the likely clinical features of SLE, and may help the generalist to recognise these children. It is promising for the future that an increasing number of black children are being recognised and referred to tertiary care institutions for management.

This study was approved unconditionally by the Ethics Committee of the University of the Witwatersrand, protocol number M00/03/36.

This work was delivered as an oral presentation at the 17th Congress of the South African Rheumatism and Arthritis Association, held in Pretoria, South Africa, 31 March - 2 April 2001.

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