

Use of Metformin in Pregnancies with Diabetes : A Case Series from India

Sir,

There have been a few publications showing that oral hypoglycaemic agents (OHA), especially metformin may be useful in the treatment of gestational diabetes.^{1,2} The safety and efficacy of the drug were consistently seen in women with the polycystic ovary syndrome (PCOS).³

In the light of the above observations, we undertook a pilot study to evaluate its advantage and safety in Indian pregnant women with diabetes.

Nine pregnant women seen during a period between June 2002 to July 2003, gave informed consent to participate in the study. Their age ranged from 24-35 years. The study was approved by the ethics committee of the institute. Four of them were known cases of type 2 diabetes and were receiving metformin (1000mg/day) therapy prior to conception. The other five were gestational diabetic (GDM) cases. Three women opted to continue using metformin and the other 6 women were advised to use only mixtard insulin from the day pregnancy was confirmed. The clinical details are shown in the table. Metformin 500 to 850 mg/day was added in the 2nd trimester (5-7th month of pregnancy) when they were referred to the centre by their gynaecologists. Seven women were overweight (BMI > 25kg/m), as judged by the pre-conception weight. With the treatment that HbA_{1c} values ranged from 5.05% to 7.5%. All of them had full-term delivery, by caesarean section. All except one baby (5.5 kg) were of normal birth weight (2.7 to 3.3 kg). The known diabetic cases continued treatment with metformin after the delivery. Among the GDM cases, 2 women continued to have diabetes on post partum oral

GTT and they were also prescribed metformin therapy. Among the other three, one had impaired glucose tolerance and two others had normal glucose tolerance on post partum assessment. They were advised diet modification and regular physical activity.

This preliminary study showed that metformin was safe in pregnant, glucose intolerant women either as an adjunct to insulin treatment or even as a monotherapy. It did not increase the occurrence of foetal macrosomia nor had teratogenic effects when used throughout the pregnancy in known cases of diabetes.

It is observed that among PCOS women who received metformin before conception continuation of the treatment throughout pregnancy reduced risk of gestational diabetes.³ It also prevented first trimester spontaneous abortion and congenital defects were also absent.

In another large cohort of pregnant women with glucose intolerance, metformin and glibenclamide were used successfully.¹ Recently Hague *et al*, conducted a pilot study in 30 women with GDM and found that the perinatal outcome of the women treated with insulin or metformin were similar.² A larger trial on the use of metformin in gestational diabetes has been started by the same group. Studies which have tested the safety of metformin during pregnancy have shown that it is safe except for only one study in Denmark⁴ which showed that use of metformin may increase preeclampsia and prenatal mortality.

A Ramachandran*, **C Snehalatha****,
S Vijayalakshmi***, **V Vijay******

*Director; **HOD of Biochemistry; ***Physician; ****Joint Director, Diabetes Research Centre and M.V. Hospital for Diabetes, WHO collaborating centre for Research, Education

Table 1 : Details of study subjects

Serial Number	Age Years	F.H.	BMI kg/m ²	Drugs	HbA _{1c} (%) at follow up	Birth weight of baby (kg)	Postpartum glucose tolerance
1	28	+	24.0	Metformin	6.9	2.8	DM
2	29	+	32.8	Metformin	7.5	3.0	NGT
3	24	+	31.7	Metformin + Insulin	7.5	3.7	NGT
4	24	+	39.9	Metformin	5.5	3.0	DM
5*	30	+	25.0	Metformin + Insulin	6.9	3.7	DM
6	27	+	27.8	Metformin + Insulin	6.1	5.5	IGT
7*	31	-	38.2	Metformin + Insulin	6.8	2.7	DM
8*	29	+	27.4	Metformin + Insulin	6.9	3.0	DM
9*	35	+	24.0	Metformin	5.5	3.25	DM

*Known Type 2 diabetes on Metformin, F.H. Family history of diabetes.

and Training in Diabetes, 5 Main Road, Royapuram, Madras 600 013.

Received : 30.7.2004; Revised : 28.10.2004;

Accepted : 21.12.2004

REFERENCES

1. Coetzee E, Jackson W. The management of non-insulin-dependent diabetes during pregnancy. *Diab Res Clin Pract* 1986;281-287.
2. Hague WM, Davoren PM, Olver J, Rowan J. Metformin may be useful in gestational. *BMJ* 2003;326:762-763.
3. Glueck CJ, Wang P, Kobayashi S, Philips H, Siever-smith L. Metformin therapy throughout pregnancy reduces the development of gestational diabetes in women with polycystic ovary syndrome. *Fertil Steril* 2002;77:520-25.
4. Hellmuth E, Damm P, Molsted-Pedersen L. Oral Hypoglycaemic agents in 118 diabetic pregnancies. *Diab Med* 2000;17: 507-511.

Valproate-Induced Hyperammonemic Encephalopathy

Sir,

The article "valproate-induced hyperammonemic encephalopathy" was read with interest and we also want to report two cases seen during last one year. Sodium valproate associated hyperammonemic encephalopathy is less a common entity and is diagnosed with high clinical suspicion.

Case One was 30 years female who was on sodium valproate 1000 mg/day for primary generalised idiopathic epilepsy since last 12 years. She was also taking ayurvedic drug (Neeraj clinic). She presented to us in status epilepticus, patient was loaded with DPH (Diphenyl hydantion) 15 mg/kg and midazolam. A day later patient was seizure-free and became conscious with no localizing neuro deficit, patient was on phenytoin 30 mg/day, sodium valproate 1000 mg/day and clonazepam 1 mg/day. Three days later patient started behaving abnormally, abusing and irrelevant episodically, 12 hours later became comatosed. Routine blood biochemistry was normal including liver enzymes serum ammonia was 170 µg/dl sodium valproate was withdrawn and phenytoin continued. Gradually patient improved over a period of 5-6 days and discharged on tenth day.

Case Two : A 40 years adult male suffering from secondary epilepsy (tubercular meningitis with VP shunt in situ) presented to us with recurrent seizures past 7 days. He was already on phenytoin 300 mg/day. Sodium valproate was added as add on @ 20 mg/kg. Fifteen days later reported with excessive sleepiness and inability to perform activities of daily living. Patient was hospitalized and investigated, routine blood biochemistry was normal. EEG showed slowing of back ground activity, serum ammonia was 200 µg/dl. Sodium valproate was withdrawn and gradually improved and discharged after 3 days.

Both our patients had no previous history of liver disease, only after sodium valproate hyperammonemia was established, both the patients were adults and along with sodium valproate they were taking phenytoin sodium.

Harsha Bhatia*, PG Raman**

*Assistant Professor; **Professor and Head, Department of Neurology and Medicine, BHRC and SAIMS Medical College, Indore.

Received : 17.9.2004; Accepted : 28.12.2004

REFERENCES

1. Sackellares JC, Lee SI, Dreifuss EF. Stupor following administration of valproic acid to patients receiving other drugs. *Epilepsia* 1979;20:697-703.
2. Zaret BS, Beckner RR, Marini AM, Wagle W, Passarelli C. Sodium valproate induced hyperammonemia without clinical hepatic dysfunction. *Neurology* 1982;32:206-8.

Hyperkalemia - An Uncommon Cause for Flaccid Quadripareisis

Sir,

The article titled 'Severe muscle weakness in hyperkalemia' by Tapiawala S *et al* in April issue of JAPI¹ made interesting reading.

As the authors have rightly pointed out, hyperkalemia commonly presents with cardiac abnormalities and neurological manifestations are rare. However, in peripheral places, we still do see a lot of patients presenting with combinations of cardiac and neurological abnormalities secondary to hyperkalemia. It is not uncommon to see patients with renal failure presenting to the casualty with paraparesis or quadripareisis secondary to hyperkalemia as the initial manifestation and occasionally, we even see patients presenting with respiratory muscle involvement.

One of the reasons that may be attributed to this is the unawareness among the physicians of the various presentations of hyperkalemia and also the causes for it. Many a times we see patients with chronic renal failure having been prescribed potassium sparing diuretics by physicians for months together, without evaluation of serum potassium. Same is the case with prescription of ACE inhibitors and NSAIDs to these patients. Both these drugs are common precipitants of raised serum potassium. Occasionally, a bout of diarrhea precipitates hyperkalemia in patients with renal failure. ECF volume contraction secondary to diarrhea, further reduces the GFR and the proximal tubular sodium reabsorption is enhanced. The decreased delivery of sodium to the distal tubules diminishes the urinary excretion of potassium and consequently serum potassium is increased.² Acutely developing urinary obstruction also precipitates hyperkalemia. This is because of a defect in distal tubular sodium reabsorption which impairs K⁺ and H⁺ secretion (voltage defect) and also hyporeninemic

hypoaldosteronism.³

I commend the authors for highlighting through their case that the importance of a timely diagnosis and treatment as even severe cases of hyperkalemia with respiratory paralysis and or near-fatal cardiac arrhythmias usually completely reverse with the lowering of serum potassium levels.

YJ Anupama

Consultant Physician and Nephrologist, Nanjappa Hospital, Kuvempu Road, Shimoga 577201, Karnataka.

Received : 5.8.2004; Accepted : 28.12.2004

REFERENCES

1. Tapiawala S, et al. Severe muscle weakness in hyperkalemia. *J Assoc Physicians India* 2004;52:505-506.
2. Rose BD, Theodore W. Post : Clinical Physiology of Acid-Base and Electrolyte Disorders; 5th Ed .McGraw-Hill, 2001;888-933
3. Kevin M Finkel, Thomas D Dubose. Metabolic Acidosis. In Dubose, Hamm (Ed): Acid-base and Electrolyte Disorders: A Companion to Brenner and Rector's The Kidney. Saunders Elsevier, 2002: 55-56.

Reply from the Author

Sir,

We are happy that Dr. Anupama found our case report interesting. Dr. Anupama brings out an important issue that in peripheral places neurologic manifestations of hyperkalemia are seen even more often. This is most likely because serum potassium is not routinely monitored in peripheral places. We hope our case report will create more awareness about hyperkalemia and make the physicians look for it in patients presenting with weakness. As pointed out by Dr. Anupama, prompt correction of potassium completely reverses the abnormalities.

BV Shah

Head, Department of Medicine and Head, Section of Nephrology, PD Hinduja National Hospital and Medical Research Centre, VS Marg, Mahim, Mumbai 400 016.

Received : 26.8.2004; Accepted : 28.12.2004

Leptospirosis with Transverse Myelitis

Sir,

Leptospirosis is a worldwide zoonosis of the greatest public health importance in the tropics. Infection may be asymptomatic, but can be fatal in 5-15% of cases. Renal failure, jaundice, myalgia, pulmonary haemorrhage, coagulopathy, myocarditis are the most usual complications. Aseptic meningitis, acute disseminated encephalomyelitis and late uveitis are rare complications.¹⁻³

A 44 year old agriculturist presented with history of fever for 14 days, retention of urine since 2 days. Fever was high grade associated with chills and rigor and generalised body pain. He was admitted in a local hospital, where he developed jaundice. Twelve days after

the onset of fever he had inability to pass urine, for which he was catheterised. Next day he developed progressive weakness of lower limbs and could not stand. Also he reported that he was unable to feel his clothes below the nipples. He was constipated since the time of urinary retention. He was a known case of hyperthyroidism on Neomercazole 10mg/day. On examination he was icteric. Vital signs were stable. CNS examination revealed hypotonia in both the lower limbs with grade 3/5 power. Abdominal, cremasteric reflexes were absent with bilateral Babinski response. Deep tendon reflexes were exaggerated. All modalities of sensation were decreased by 50% below T₄ level. Meningeal signs were absent. Fundus examination was normal. Other systems were normal. A probable diagnosis of leptospirosis with post-infectious transverse myelitis was made. MRI brain and spinal cord was normal. Hb was 14.6 g/dl, WBC 16,900/mm³ with N 85%, L 13%, and M 2%. Urine protein was trace, sugar nil, WBC 2-3/hpf, RBC 60-80/hpf, granular casts present. ESR was 90 mm/1st hour. CSF protein was 59 mg/dl, sugar 78 mg/dl (corresponding blood sugar was 126mg/dl.), total WBC 15 cells/mm³ with 91% lymphocytes and 9% polymorphs with fasting glucose was 116mg/dl, total bilirubin 7.6mg/dl, direct bilirubin 5.9mg/dl, AST 63U/L, ALT 92U/L, ALP 160U/L. Anti HAV, HBs Ag and anti HCV were negative. IgM anti-leptospira antibody was positive (15 pan biounits).

He was diagnosed to have leptospirosis with transverse myelitis. He was given parenteral crystalline penicillin, doxycycline 100 mg bd and intravenous methyl prednisolone 1g for 5 days. Later 1mg/kg of wysolone was given from day 6 to 17, followed by 20 mg from day 18 to 20 and 10 mg on day 21. His hepatic functions improved gradually and was normal at discharge. He improved remarkably and he was able to walk without support. Urinary catheter was subsequently removed and he remained continent.

Transverse myelitis is an acute or subacute, generally monophasic, inflammatory disorder of the spinal cord. It results from an autoimmune response triggered by an infection or recent vaccination. Many infectious agents have been implicated, including influenza, measles, varicella, rubeola, mumps, EBV, CMV, as well as mycoplasma.⁵

Pathological changes include subpial and perivenular zones of demyelination, with perivascular and meningeal infiltration of lymphocytes. CSF contains lymphocytes in the range of 10-100/mm³, with slightly raised protein and normal glucose content. MRI findings include variable swelling of the cord along with T2 signal abnormalities often extending over multiple segments and slight gadolinium enhancement. MRI may be normal in mild or partial myelitis. The prognosis is good in purely myelitic disease, but in some cases sequelae have been severe and permanent.

Leptospiraemia lasts from 4 to 7 days and ends when

the agglutinating antibodies appear. Much of the pathogenesis of leptospirosis remains unexplained. Fatally infected animals and some humans exhibit changes similar to those produced by endotoxaemia of Gram negative bacteria. Symptoms of meningitis coincide with the development of antibody and disappearance of leptospira from blood and CSF, suggesting an immunological mechanism. Transverse myelitis is a result of disordered immune regulation, probably leptospira acting as inciting agents for the disordered immune response. This patient's weakness started 10 days after the fever onset, correlating well with the immune phase. Leptospira could not be demonstrated in blood or CSF, as is expected in the second phase of the illness. In conclusion, transverse myelitis has to be kept in mind as an unusual complication of leptospirosis.

S Kavitha*, BA Shastry**

*Assistant Professor; **Professor, Department of Medicine, Kasturba Medical College, Manipal.

Received : 10.8.2004; Revised : 13.10.2004;

Accepted : 28.12.2004

REFERENCES

1. George W. Leptospirosis. In: David A Warrell, Timothy M Cox, John The Firth, Edward J Benz, Jreds Oxford Textbook of Medicine Fourth edition. Oxford university pres, New York: 2003: 600-604.
2. Peter S. Leptospirosis. In: Braunwald, Fauci, Kasper, Hauser, Longo, Jameson eds. Harrison's Principles of Internal Medicine, Vol 1,15th edition, Mc Graw-Hill:1055-1058.
3. Jagadishandra K, Prathab AG, Rao SP. Clinical and epidemiological correlation of leptospirosis among patients attending KMCH, Manipal. *Ind J Med Sci* 2003; Vol 57, No 3:101-104.
4. Chandra SR, Kalpana D, Anil Kumar TV, Kabir KA, Chitra P, Rani Bhaskaran. Acute disseminated encephalomyelitis following leptospirosis. *JAPI* 2004;52:327-329.
5. Stephen L Hauser. Diseases of the spinal cord. In: Braunwald, Fauci, Kasper, Hauser, Longo, Jameson eds. Harrison's Principles of Internal Medicine, Vol 2, 15th edition, Mc Graw-Hill: 2425-2434.

Conjunctival Mass : Rare Site of Extramedullary Relapse in Childhood Acute Lymphoblastic Leukemia

Sir,

A 2-year old boy presented with pallor requiring blood transfusions. He was diagnosed as acute lymphoblastic leukemia (ALL) outside based on bone marrow examination. He was started on induction chemotherapy with prednisone, vincristine and L-asparaginase, following which he improved symptomatically but then discontinued treatment after six week. Six months later, he presented to our institute with fever, swelling over the forehead and left eye (Fig. 1). On physical examination, he had a mass in the left supero-lateral palpebral conjunctiva with surrounding conjunctival



Fig. 1 : Showing right supraorbital and left eye swelling.



Fig. 2 : Showing salmon patch conjunctival involvement superiorly and temporally associated with recurrent acute lymphoblastic leukemia.

injection (Fig. 2). Fundus examination was normal. The swelling over the forehead was 1 cm in size above the right supraorbital region; it was firm, nontender and mobile. There was no hepatosplenomegaly. Bilateral testes were enlarged and hard in consistency. Peripheral smear examination showed blasts that were negative for myeloperoxidase thereby confirming as relapse of ALL. Cerebrospinal fluid examination also showed presence of blasts. Thus, the patient had bone marrow relapse and extramedullary relapse of ALL in central

nervous system, and clinically as well in the testes, skin and palpebral conjunctiva. Patient was started on 4-drug induction chemotherapy consisting of prednisone, vincristine, daunorubicin and L-asparaginase along with intrathecal methotrexate. Within 3 days of starting chemotherapy, the testicular swelling, conjunctival mass and right supraorbital swelling subsided and almost disappeared by day 6 of chemotherapy. The patient, however, decided to discontinue therapy after 2 weeks and was then lost to follow up.

The most common sites of extramedullary relapse in ALL are central nervous system and testes. Unusual sites of extramedullary relapse have been described in childhood ALL such as that in the cervix, kidneys, middle ear, pleura and bone. Leukemic manifestations in the eye most often occur in the retina; external eye involvement is unusual but is notable as a rare site of extramedullary relapse. Conjunctival tumours have been known as a site of relapse in acute myelomonocytic leukemia;¹ however, there is only one report of childhood ALL presenting as conjunctival mass,² and one other similar case reported in adult literature.³ Thus, it may be reasonable to consider leukemic relapse in patients presenting with a conjunctival mass and a previous history of leukemia.

S Bakhsi*, LS Arya**

*Assistant Professor, Pediatric Oncology, Dr. BRA Institute Rotary Cancer Hospital; **Department of Pediatrics, All India Institute of Medical Sciences, New Delhi.

Received : 2.8.2003; Accepted : 1.1.2005

REFERENCES

1. Lei KI, Liew CT, Lam DS, Chan AT, Wickham NW. Acute monoblastic leukaemia with conjunctival tumours. *Clin Oncol* 1996;7:405-6.
2. Campagnoli MF, Parodi E, Linari A, D'alonzo G, Onnis E, Farinasso L. Conjunctival mass : an unusual presentation of acute lymphoblastic leukemia relapse in childhood. *J Pediatr* 2003;142:211.
3. Cook BE Jr, Bartley GB. Acute lymphoblastic leukemia manifesting in an adult as a conjunctival mas. *Am J Ophthalmol* 1997;124:104-5.

Three Year Study of Antibiotic Resistance in Acinetobacter Species Isolated from Clinical Specimens

Sir,

Acinetobacters are predominant nosocomial pathogens of growing importance that have been recognized as opportunist pathogens causing bacteraemia, pneumonia, wound and urinary tract infections.¹ Worldwide reports have shown that majorities of Acinetobacters are multi-drug resistant and difficult to control and treat.²

This retrospective study was done to see the in-vitro activity of 582 Acinetobacter strains isolated from pus and urine samples over a period of three years (June

2000 - May 2003). About 85% of pus samples constituted tracheal aspirates from ventilated patients and rest 15% were body fluids, sputum and wound aspirates. 83% of the urine samples were from indoor catheterized patients. In vitro antibiotic susceptibility was determined by Stokes disc diffusion method against routinely used antibiotics like amikacin, augmentin, third generation cephalosporins, ciprofloxacin, tobramycin and newer antibiotics like imipenem, cefdinir, cefepime and combination antibiotics like piperacillin-tazobactam and cefoperazone-sulbactam.

In total, 85.6% of the isolated strains of Acinetobacters were from indoor patients. Amongst the pus isolates, saccharolytic Acinetobacters (80%) was the predominant type while in urine samples 58% were saccharolytic Acinetobacter and 42% were asaccharolytic type. For pus isolates, the yearly trend shows the statistically significant rise in resistance ($p < 0.05$) to the following antibiotics, like ceftriaxone, ceftazidime, carbenicillin, amikacin, gentamicin and ciprofloxacin. For urinary isolates, rising pattern of resistance was observed only for ciprofloxacin where $p < 0.05$ was noted. Out of the total pus isolates, only 2% showed resistance to imipenem, 3% to cefoperazone-sulbactam and 6% showed resistance to piperacillin-tazobactam. None of the urinary strains were found to be resistant to imipenem and cefoperazone-sulbactam.

Members of the genus Acinetobacter are increasingly being implicated in hospital acquired infections mostly affecting debilitated patients such as in ICU's where risk factors for colonization and infection include mechanical ventilation, hyperalimentation, peripheral or arterial catheterization and antibiotic therapy. In our three year study period, increasing resistance of Acinetobacter spp. to various groups of antibiotics was observed (β -lactams including newer generation of cephalosporins, aminoglycosides and flouroquinolones). In - vitro testing of cefepime and ceftazidime also showed 100% resistance as shown in an earlier study that emerging β -lactamases progressively compromises the use of β -lactam compounds. This high resistance to β -lactams may be because of hyperproduction of chromosomal Amp-C type enzyme plus porin mutations or production of OXA and metallo-beta lactamases which break and inactivate β lactam drugs.³ Gatifloxacin was used in few isolates from pus and it showed 18% resistance only.

In our study all of the isolates from urine were susceptible to imipenem and only 2% resistance to imipenem was seen amongst pus isolates. Resistance to imipenem may be either due to chromosomal/plasmid mediated beta lactamases or porin protein mutations.

The use of β -lactamase inhibitors in combination with β lactam drugs is the strategy used these days to combat drug resistance. Our results also depict very low level of resistance to combination antibiotics like cefoperazone-sulbactam and piperacillin-tazobactam.

Hence we conclude from our study that *Acinetobacter* species are important causes of hospital associated infections. The results obtained regarding the antibiotic resistance pattern for most of the routinely used antibiotics show a rising trend of resistance. However, imipenem and combination antibiotics are still effective for therapy. Surveillance of antibiotic use and formulation of antibiotic policy is mandatory to prevent indiscriminate use of these drugs and emergence of drug resistance.

Varsha Gupta*, **Neelam Kaistha****, **Nalini Agnihotri****, **M Singh*****, **Priya Datta*****

*Reader; **Senior Lecturer; ***Demonstrator, Department of Microbiology, Government Medical College and Hospital, Sector-32 B, Chandigarh.

Received : 15.5.2004; Revised : 4.10.2004; Accepted : 23.12.2004

REFERENCES

1. Crowe M, Towner K, Humphreys H. Clinical and epidemiological features of outbreak of *Acinetobacter* infection in an intensive therapy unit. *J Med Microbiol* 1995;43:55-62.
 2. Wisplinghoff H, Edmond MB, Pfaller MA. Nosocomial blood stream infections caused by *Acinetobacter* species in United States hospitals : clinical features molecular epidemiology and antimicrobial susceptibility. *Clin Infect Dis* 2000;31: 690-97.
 3. Nordmann P, Poirel L. Emerging carpenemases in gram negative aerobes. *Clin Microbiol Infect* 2002;8:321-31.
-

Bilateral Ptosis Following Wasp Sting

Sir,

This is with reference to HS Bawaskar's correspondence¹ on the article "Bilateral ptosis following wasp sting" by Singh RD *et al.*² I would like to point out that in the cause of a wasp sting, the stinger is almost never left behind at the site, while this is usually true of a bee sting. The reason is simple. In the case of the former, the stinger is smooth; hence it slides easily in and out. In the case of the bee however, the stinger is barbed; hence, while the entry is easily facilitated, the exit is tough owing to the barbs getting caught in the tissue.³ In fact, often in its frantic attempts to withdraw the stinger the bee eviscerates itself! Wasps do not face such a problem, and that is why repeated stings are common with wasps, while it is very rare in the case of bees.

VV Pillay

Chief, Poison Control Centre, Amrita Institute of Medical Sciences, Cochin 682026.

Received : 26.11.2004; Accepted : 1.1.2005

REFERENCES

1. Bawaskar HS. Bilateral ptosis following wasp sting (Letter). *JAPI* 2004;52:842.
 2. Singh RD, Bhagat A, Pandey AK. Bilateral ptosis following wasp sting. *JAPI* 2003;51:828-29.
 3. Pillay VV. Venomous bites and stings. In : Comprehensive Medical Toxicology. Hyderabad : Paras Medical Publisher. 2003;548-90.
-