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Tetanus from Intramuscular Quinine Injection In Warri Niger Delta. Case series: A ten year retrospective study

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Summary *Aim* To evaluate the development of tetanus from intramuscular injection in children in Warri, Niger Delta of Nigeria
Materials and Method: Retrieval and analysis of case notes of all children with tetanus seen between 1999 and 2008 at Central Hospital Warri with referrals from surrounding General Hospitals and GN Children's Clinic one of the four private hospitals for children in Warri and its environs, and noting those resulting from intramuscular injections.
Results: A total of one hundred and seventy five children were diagnosed with tetanus with twelve due to intramuscular injections. Out of the twelve, ten were from intramuscular quinine injection giving a per centage of 83.3%. Six out of the ten from intramuscular quinine were males. The case fatality rate in males is 100% but 50% in females. The patients were given the injections mainly in private clinics and the remaining from a chemist store. The incubation period in all of them was less than seven days. Only one of the patients with tetanus from intramuscular quinine injection survived, giving a mortality rate of 80%.
Conclusion: Tetanus from intramuscular quinine in children is relatively uncommon probably because less usage of that route for quinine administration. However, when it occurs, it is highly fatal. Other routes of parentheral quinine administration such as intrarectal are recommend. There is however a recent WHO giudelines on the treatment of severe falciparum malaria which showed the superiority of intravenous artesunate over quinine

Introduction

Tetanus is a vaccine preventable but non-contagious disease and is frequently fatal in extreme of ages and in resource poor countries[1]. The disease has been known as far back as the period of early Egyptian civilization over three thousand years ago[2].It is caused by the second most potent neurotoxin called tetanospasmin, which is produced by the organism *Clostridium tetanii*. This is a spore-forming gram positive strictly obligate anaerobe, whose spores are resistant to heat, disinfectants and other chemicals, and is found worldwide, present in soil and the dung of some animals[3]. It enters the body through various portals, but for germination to occur, the bacillus needs low oxygen-reduction (redox) potential such as that associated with necrosis and proliferation is enhanced by the presence of blood, foreign bodies, and chemicals such as lactic acid, calcium salts and quinine[4]. Malaria is endemic and severe in these developing countries and the malaria parasite has become very resistant to various antimalarias including chloroquine and suphomethoxazole-pyrimethamine combination[5]. Several treatment regimens have been formulated in various countries to overcome this resistance including intramuscular, oral, and slow intravenous infusion of quinine[6], [7, 8]. Each of these routes of administration of quinine has its own complications and one of the complications

of intramuscular quinine injection is tetanus[9]. We report twelve cases of tetanus following intramuscular injection, of which ten of the cases followed quinine injection in children in Warri Niger delta of Nigeria over a ten year period from 1999 to 2008. The study was carried out at Central Hospital Warri which is the government specialist hospital, serving three local government areas with a combined population of two million three hundred and fifty according to the 2006 Nigerian population census[10]. The study was also carried out at GN Children's Clinic which is one of the four private children's hospitals in the same area.

Materials and Method

Retrieval of the case notes of all children admitted with tetanus at the Central Hospital Warri and GN Children's Clinic between January 1999 and December 2008 was carried out. The case notes were then analyzed. Information obtained included among other things, the age, sex of each patient, presenting symptoms, portal of entry of the organism, place of initial presentation before referral to these centres if any, duration of the illness, perinatal records (place and method of delivery etc), immunization status of the child, social background (occupation of parents, place of domicile, was the child attending school? Etc), any treatment given for the illness before presentation, past medical history, clinical signs, management given to the children in these hospitals and the outcome of the illness. Follow up treatment for each of the patients was also noted.

Results

Of the one hundred and seventy five patients seen, only in twelve of these children was the portal of entry through intramuscular injections (6.9%). Of these twelve patients, ten were from intramuscular injection of quinine giving a per centage of 83.3% tetanus from intramuscular injection. Six of the patients were males, giving a male: female ratio of 3:2. Eight out of the patients died, giving a mortality rate of 80%. Of the eight that died, six were males. So the case fatality rate in males of 100% and females 50%. we report five cases.

Case1

This is a five year old boy who presented in a private clinic with fever, chills, vomiting, loss of appetite and abdominal pains He was given oral drugs, all of Which he vomited. He was then placed on 12hourly intramuscular injection of quinine for five days. He recovered from the illness, an five days later developed generalized spasms with inability to open his mouth. The spasms were unprovoked. He had two doses of DTP in infancy. He was found on examination to be in pains but conscious with rhesus sardonicus. Frequent unprovoked spasms were observed. The child was well nourished with a temperature of 37.9°C. A diagnosis of severe generalized tetanus was made with meningitis as a differential. Investigations showed he had normal blood glucose level and all other laboratory parameters were normal.

He was started on 8% dextrose infusion. Antitetanus serum 20, 000IU was given, with 10, 000IU given through the infusion and the other 10, 000 IU intramuscularly. This was given after test dose. He was also given intravenous Ceftriazone 100mg/kg and metronidazole infusion. The antibiotic was to procaine penicillin given intramuscularly as a single daily dose. This was after 48hours on admission. He was also stared on intravenous diazepam .5mg/kg 6hourly, staggered with phenobarbitone 5mg/kg 6hourly. The sedatives were given in such a way that he receives a sedative every 3hours. Paraldehyde 1ml/age in year to a maximum dose of 5ml in childhood (he got 4ml) was given for breakthrough seizures. The spasms continued and he died on the eighth day of admission despite increasing the dose of the diazepam and even changing to chlorpromazine. Human immunoglobin was not available

Case 2

This was a ten year old boy who developed fever, vomiting, chest pain loss of appetite and headache. He was taken to a chemist store where he was given daily quinine injection for six days, in addition to some oral tablets. He apparently recovered but one eight days after the last injections, he complained of jaw pains and a day later he was unable to open his mouth which was then followed with generalized spasms. He took the immunization according to EPI schedule. He was first taken to a nearby General hospital where he stayed for three days before being referred to GN children's clinic. He was found on examination to be conscious in pains, with frequent unprovoked spasms. The management was generally along the line of the first case but had to be transfused twice. He also developed measles while in the hospital and also a massive scalp sore. He recovered gradually and was discharged after fifty days of admission. At some point in time, the antibiotic was changed to intravenous ciprofloxacin.

Case 3

Master T was a seven and a half year old boy who developed fever abdominal pains and loss of appetite and rigors. He was taken to a private hospital where he was started on 12hourly quinine injections because he does not like to take drugs. He had the injections for five days but developed unprovoked spasms three days after the last quinine injection and was unable to open his mouth He had the immunization according to EPI in a health centre. He was diagnosed as having generalized tetanus. He was treated along the line of the first patient. Unfortunately, he died four days after admission.

Case 4

She was a nine year old primary five pupil who developed headache, fever chills deep amber urine and generalized body pain. The attending Doctor placed her on quinine injection for two days and oral quinine thereafter for another five days. She recovered and continued her studies. Seven days after the last quinine injection, she was unable to open her mouth which was later followed with frequent spasms. She was first taken to the initial doctor who diagnosed tetanus and referred her to Central hospital Warri. She was again treated along the line of the first patient. The frequency of the spasms seemed to be reducing but she died two weeks after presentation.

Case 5

He was five years three months and five days old. He had fever which the mother had been treating with various antimalaria drugs namely, chloroquine syrup, sulphadoxine-pyrimethamine prep by roche and halophantrin, and was even given amoxicillin-clauvulinic acid syrup all to no avail. Because of the persistence of the fever, he was taken to a private hospital where he was started on intramuscular quinine after laboratory tests showed he had malaria. About three days after the injections, he developed generalized body stiffness with recurrent spasms. He was immunized according to the EPI schedule. He was found to be conscious and crying in pains and spasms observed. He was diagnosed as having generalized tetanus and was managed generally along the line of the first patient but unfortunately died on the seventh day of admission.

The two patients with tetanus from intramuscular injection other than quinine were female who received intramuscular anlgin and diclofenac sodium injection respectively, but happily, they survived.

Discussion

Tetanus arising from intramuscular quinine injection has been reported in the medical literature even in the early and middle part of the 20TH century, [11,12]. Though it can occur from intramuscular injections of other substances, it is predominant with intramuscular quinine. A study in Dakar Senegal that out of forty six cases of tetanus from intramuscular injection, the substance given was identifiable in thirty three of them, out of which quinine was the cause in thirty two of them [13].

The study was in adults. The number of twelve cases seen here over a ten year period is relatively small compared to the number in that study. This is probably because children still have some immunity from immunization in infancy compared to adults. In our study, the incidence is relatively more common in the older child. The mean age group from the Dakar study is 34.5years.[13]. Moreover the incidence may be lower because of less use of intramuscular quinine as opposed to countries like Vietnam and Congo where it is a major form of malaria treatment[14,15]. One of the hypothesis for quinine as a cause is that quinine causes severe tissue necrosis when given through that route which is a good medium for the clostridia organisms, [11,16,17]. Infact in trying to experiment on the effect of the tetanus toxin, quinine salt solution is used as a substrate[4]. Quinine is also known to potentiate the neurotoxic effects of botilinum and tetanospasmin, the two most potent neurotoxins[18].

One notable observation in our study is that the onset interval for most of the patients is less than one week. In the study in Senegal the mean onset interval is 48hours.[13] Most of the patients are males and this is the same experience even in adult[13,19]

The mortality in our study is very high at 80% which is higher than the overall mortality of childhood mortality from tetanus within the same period and in the same study area[20]. Even the case fatality is much higher than neonatal tetanus in the same area[21]. The mortality rate of 80% is closer to that observed in Vietnam at 76% but higher than that recorded in the Senegalese study with 62.5%. The study in Vietnam also showed the mortality rate compared to tetanus from intramuscular injection of other drugs was lower than with quinine[19]. The solitary patient in our study with tetanus from intramuscular injection other than quinine survived

Conclusion

Quinine remains the drug of choice for treatment of severe malaria[22]. The high fatality rate tetanus from the

administration of quinine intramuscularly as observed from many centers has made the clinicians recommend other routes[13],[15,19]. Some clinicians however argue that it may be life saving especially where venous assess if difficlut[23]. Though parentheral quinine either intravenously or intramuscularly has its various complications, studies have shown that intrarectal administration of quinine is as rapid and efficacious as intravenous quinine infussion[24]. This will eliminate the bias due to difficulty in assessing the vein and also the risk of tetanus if given intramuscularly. A prospective study is on in our centre on the use of intrarectal quinine. Recently, the World Health Organization has published a new gideline in the management of severe malaria and the superiority of inravenous arthemesimin over quininine from whatever route. It was documented that response was better with intravenous arthemesimin than quinine by upto 37% with much less combination[25]

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