CASE REPORT

Concentration-related mydriasis in a patient with renal dysfunction treated with phenytoin

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Abstract
Introduction: There is very limited evidence concerning phenytoin-related mydriasis.
Case report: A 59-year-old male was hospitalized in the intensive care unit due to a head injury. During his hospitalization, phenytoin was administrated. Some days later he presented bilateral mydriasis. At that time he had impaired creatinine clearance 7 ml/min, albumin levels 3.4 gr/dl, and phenytoin serum concentration 19.94 μg/dl. Evaluation with brain computed tomography and magnetic resonance imaging did not reveal any potential cause of mydriasis, while none of the co-administrated drugs have been reported to cause significant mydriasis. After initiation of continuous venovenous hemodiafiltration and discontinuation of phenytoin, mydriasis was reversed.
Conclusion: Clinicians should be aware that mydriasis due to a toxic concentration of phenytoin may be manifested.
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Keywords: Phenytoin, concentration-related, mydriasis, renal dysfunction, adjusted concentrations

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Introduction

Medications cause mydriasis either by stimulation of the sympathetic innervations of the dilator papillae or inhibition of the parasympathetic innervations to the sphincter papillae. Examples include parasympatholytic cycloplegic drugs, sympathomimetics such as adrenaline, phenylephrine, clonidine and rarely brimonidine as antiglaucoma medication. Other autonomic medications such as scopolamine patch used for motion sickness can also produce pharmacologic mydriasis[1-2]. Moreover, aerosolized anticholinergic drugs such as ipratropium have also been reported to cause unilateral mydriasis[3-5]. Pharmacologic mydriasis is not associated with pain, ptosis or diplopia.

Case Report

A 59-year-old male patient with free past medical history was admitted to the intensive care unit (ICU) due to traumatic brain injury. The patient underwent brain computed tomography (CT) scan on admission, which revealed bilateral contusion lesions and received levetiracetam intravenously for seizure prophylaxis. All administered medications are displayed in Table 1. The patient had Glasgow Coma Scale (GCS) 10/15, during the first 48 hours after his admission. On the third day his neurological status deteriorated (GCS: 7/15), and he was intubated. On the fourth day the patient became febrile and hemodynamically unstable; *Klebsiella pneumoniae* was isolated from bronchial secretions and he received combination therapy with colistin and gentamicin for 14 days. The patient showed gradual improvement of his neurological status, became afebrile with good gas exchange, and was extubated at day 13 of his hospitalization. The next day the patient developed seizures and was intubated again. Until then the patient had normal hepatic and renal function with the values of serum creatinine ranging from 0.5-0.7 mg/dl and serum urea ranging from 29-44 mg/dl. On day 19 phenytoin administration was initiated, and from day 19 to day 24 the serum creatinine and urea values gradually increased up to 0.9 mg/dl and 159 mg/dl, respectively. Moreover, the patient became hemodynamically unstable necessitating administration of noradrenalin and combined antibiotic therapy with colistin and tigecycline as indicated according to microbiology cultures for possible infection (Table 1). On day 21 total phenytoin blood levels were 17.04 μg/dl (within the therapeutic range and with normal albumin levels 3.8 gr/dl). The patient developed gradual deterioration of his neurological status with bilateral mydriasis (pupil's diameter: 8 mm, not reacting to light), and was intubated due to coma on day 24. Imaging evaluation with brain CT and magnetic resonance imaging (MRI) scans did not

Table 1: Administrated drugs during hospitalization in the intensive care unit of a 59-year-old male due to a head injury. On the third day he was intubated and on the fourth he became febrile and hemodynamically unstable. He was extubated at day 13 and the next day he developed seizures and was intubated again. On day 19 phenytoin administration was initiated, and later the patient became hemodynamically unstable necessitating administration of noradrenalin and combined antibiotic therapy with colistin, tigecycline as indicated according to microbiology cultures for possible infection. On day 24 he was intubated due to coma and developed bilateral mydriasis (pupil's diameter: 8 mm, not reacting to light).

Drug/Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
Dopamine IV	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			
Noradrenaline IV				x	x	x	x	x	x	x													x	x	x					
Amiodarone IV	x	x	x	x														x	x	x	x	x	x	x	x	x	x	x	x	x
Propofol IV			x	x	x	x	x	x	x	x	x	x		x	x									x	x	x				x
Remifentanil IV			x	x	x	x	x	x	x	x	x	x		x	x									x	x	x				x
Omeprazole IV	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x										
Budenoside INH	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Leviracetam IV	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Meropenem IV		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x													
Gentamicin IV				x	x	x	x	x	x	x	x	x	x	x	x	x	x					x	x	x	x	x	x			
Metoclopramide IV					x	x	x	x	x	x	x	x	x	x	x	x	x													
Furosemide IV						x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Dexamethosone IV							x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			
Enoxaparin SC									x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x					x	x
Tigecycline IV																				x	x	x	x	x	x	x	x	x	x	x
Colistin IV				x	x	x	x	x	x	x	x	x	x	x	x	x	x			x	x	x	x	x	x	x	x	x	x	x
Phenytoin IV																			x	x	x	x	x	x	x					
Ranitidine IV																					x	x	x	x	x	x	x	x	x	x
Fluconazole IV																											x	x	x	x
Bivalirudine IV																									x	x	x	x		

IV: Intravenous, SC: Subcutaneous, INH: Inhaler

reveal any new abnormal findings. At that time, his renal function was impaired (serum creatinine: 2 mg/dl, urea: 273 mg/dl, creatinine clearance: 7 ml/min) while the total phenytoin blood level was 19.94 μg/dl and albumin level 3.4 gr/dl. The following day mydriasis persisted. Reevaluation with brain MRI scan didn't show any new findings. Serum creatinine and urea values reached 2.2 mg/dl and 290 mg/dl, respectively; the patient was set on continuous venovenous hemodiafiltration (CVVHDF), and phenytoin administration was discontinued. The patient remained under CVVHDF for four days. His clinical condition gradually improved with reversal of mydriasis within hours of CVVHDF initiation, improvement of his neurological status (GCS: 12/15), hemodynamic condition, and renal function. Moreover, phenytoin blood levels decreased to 15.00 μg/dl. On day 27 the patient was extubated and on day 28 CVVHDF was stopped due to further amelioration of his renal function (creatinine clearance: 33 ml/min). No severe electrolytes or metabolic abnormalities were detected during his hospitalization in ICU. After two days the patient was transferred to a medical ward and discharged from hospital ten days later with no mydriasis. After his discharge from hospital no follow up information is available.

Discussion

According to the European database of suspected adverse drug reactions, 12 cases of phenytoin-related mydriasis have been reported[6]. Based on the above reports we hypothesized that phenytoin could be the cause of mydriasis in our patient. It might be argued that mydriasis could be due to administration of other agents or due to patient's neurological deficit. More specifically, sympathomimetics drugs may cause mydriasis (reported patient had been receiving dopamine for 20 days and norepinephrine two days before the onset of mydriasis), but with a papillary diameter of 1-2 mm (reported patient had 8 mm). The dose of antibiotic colistin (started one day before the onset of mydriasis) was adjusted according to the renal function of the patient. Thus, colistin levels were within therapeutic range. Gentamicin dose was also adjusted and trough concentrations were <1 mg/l. Apart from that, only phenytoin administration was discontinued at the onset of mydriasis; administration of all other medications remained unchanged from the onset of mydriasis until the recovery, with their doses adjusted to the renal function. Another confusing issue was the fact that the acute renal failure, as has been described in the literature, has an effect on the pupil's size. In this case, pupils are almost always symmetric, react to light, and symptoms reverse with dialysis but this requires one to two days[7]. However, in our case, patient's pupils did not react to light and mydriasis recovered within a few hours from the commencement of dialysis. Also, no brain lesion that could lead to bilateral mydriasis, such as cerebral edema with brain herniation or cerebrovascular accident involving the third cranial nerve, were demonstrated in consecutive brain MRI scans. Furthermore, mydriasis appeared concurrently with the elevation of phenytoin serum concentration to 19.94 μg/dl (with albumin levels 3.4 gr/dl) and decline of creatinine clearance to values less than 10 ml/min. Phenytoin has a very high affinity for plasma protein resulting in binding to proteins over 90 %. However, in cases of hypoalbuminemia and/or decreased creatinine clearance below 10 ml/min, phenytoin levels should be adjusted because the fraction of free phenytoin is increased[8]. In decreased renal function, uremia causes displacement of phenytoin from albumin and adjusted

drug levels should be calculated according to the following formula[9-11]:

$$\text{Adjusted levels} = \frac{\text{Measured total levels}}{[(0.1*\text{serum albumin})+0.1]} = 45.3\ \mu g/dl$$

So, in our case, phenytoin serum concentration was in toxic levels. As it is known, much phenytoin-related toxicity is concentration-dependent. Our hypothesis was further supported by the fact that mydriasis resolved after phenytoin discontinuation and thus decrease of its concentration, and initiation of CVVHDF that significantly improved his renal function. The scoring according to Naranjo Algorithm was equal to eight, which suggests that the likelihood that the observed mydriasis was associated with the use of phenytoin would be rated as a "probable" adverse drug reaction[12]. We suggest that clinicians should be aware of any patient with renal dysfunction and/or hypoalbuminemia treated with phenytoin who presents with mydriasis, following the reasonable exclusion of other potential causative factors of mydriasis.

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