Atypical extrapyramidal syndrome: metamizole-associated hemidystonia – A case report and review of cardiovascular implications in analgesic safety

Síndrome extrapiramidal atípico: hemidistonía asociada al metamizol – reporte de un caso y revisión de las implicaciones cardiovasculares en la seguridad analgésica

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Abstract

Drug-induced extrapyramidal syndrome usually has clinical features like dyskinesia, dystonia, akathisia, Gilles de la Tourette syndrome, myoclonus, and Parkinsonism. The most common drugs that cause drug-induced extrapyramidal syndrome are neuroleptics. Metamizole (dipyrone) is a widely used non-opioid analgesic in human medicine. Metamizole is generally considered a safe medication, though it is not entirely without potential side effects. There have been no reports of people using metamizole experiencing extrapyramidal syndrome symptoms such as hemidistonia. A 42-year-old man presented with hemidystonia and dysphasia after receiving metamizole injection. He had a similar episode in the past associated with the same medication. Neurological examination revealed hemidystonia without loss of consciousness, seizure, or headache. The patient was also being treated for pulmonary tuberculosis and had comorbid anemia, thrombocytopenia, elevated liver enzymes, hypoalbuminemia, hyponatremia, and hypokalemia. A contrast-enhanced head CT scan showed no structural abnormalities. Intravenous administration of diphenhydramine led to symptom resolution. Metamizole was discontinued, and no recurrence occurred during the follow-up period. This case highlights metamizole-associated hemidystonia as a rare but reversible extrapyramidal reaction. Clinicians should consider this potential adverse effect, especially in patients with metabolic or hepatic dysfunction.

KEYWORDS: Extrapiramidal syndrome, Hemidystonia, Metamizole.

Resumen

El síndrome extrapiramidal inducido por fármacos suele presentar características clínicas como discinesia, distonía, acatisia, síndrome de Gilles de la Tourette, mioclonías y parkinsonismo. Los fármacos más comunes que causan el síndrome extrapiramidal inducido por fármacos son los neurolépticos. El metamizol (dipirona) es un analgésico no opioide ampliamente utilizado en medicina humana. Generalmente, se considera un medicamento seguro, aunque no está completamente exento de posibles efectos secundarios. No se han reportado casos de personas que usan metamizol que presenten síntomas de síndrome extrapiramidal como hemidistonía. Un hombre de 42 años presentó hemidistonía y disfagia después de recibir una inyección de metamizol. Había tenido un episodio similar en el pasado asociado con el mismo medicamento. El examen neurológico reveló hemidistonía sin pérdida de consciencia, convulsiones ni cefalea. El paciente también recibía tratamiento para tuberculosis pulmonar y presentaba anemia comórbida, trombocitopenia, enzimas hepáticas elevadas, hipoalbuminemia, hiponatremia e hipopotasemia. Una tomografía computarizada craneal con contraste no mostró anomalías estructurales. La administración intravenosa de difenhidramina resolvió los síntomas. Se suspendió el metamizol y no se observó ninguna recurrencia durante el seguimiento. Este caso destaca la hemidistonía asociada al metamizol como una reacción extrapiramidal rara pero reversible. Los médicos deben considerar este posible efecto adverso, especialmente en pacientes con disfunción metabólica o hepática.

PALABRAS CLAVE: Síndrome extrapiramidal, Hemidistonía, Metamizol.

Introduction

Metamizole, also known as dipyrone, is a pyrazolone derivative that has been used for nearly a century as an effective non-opioid analgesic and antipyretic[1]. First synthesized in 1920, it gained rapid international acceptance due to its broad spectrum of pain-relieving activity, mild gastric irritation, and minimal sedative effect compared with other analgesics[2]. Despite its long history, metamizole remains one of the most controversial drugs in modern pharmacotherapy. It was withdrawn from the United States and several European countries following reports of fatal agranulocytosis[3], though subsequent studies have questioned the magnitude of this risk, leading to its re-approval in several nations under strict monitoring conditions[4]. It remains freely available in many countries, including Germany, Spain, Brazil, and Indonesia[5].

From a pharmacological standpoint, metamizole acts as a prodrug rapidly converted into its active metabolites—4-methylaminoantipyrine (4-MAA) and 4-aminoantipyrine (4-AA)—in the liver[6]. These metabolites inhibit prostaglandin synthesis via non-selective cyclooxygenase (COX) blockade[7]. However, recent research has revealed that metamizole's analgesic mechanisms extend beyond COX inhibition, involving modulation of endogenous cannabinoid and opioid systems, and importantly, the metabolite 4-MAA crosses the blood-brain barrier, implicating potential effects on central neurotransmission[8,9]. The global pattern of metamizole use illustrates a dichotomy between regulatory caution and clinical reliance, particularly in regions with limited access to other analgesics[10,11]. While the World Health Organization lists it as an essential medication in several contexts, it emphasizes pharmacovigilance due to possible hematologic and hepatic complications[12]. Nonetheless, its potential to induce neurological adverse effects remains largely underrecognized and represents a critical gap in safety profiles, especially relevant when treating patients with complex medical backgrounds[13].

Extrapyramidal symptoms (EPS) are a group of drug-induced movement disorders that include acute dystonia, Parkinsonism, akathisia, and tardive dyskinesia[14]. They arise from dysfunction within the basal ganglia, specifically the nigrostriatal dopaminergic pathway[15]. When dopaminergic signaling is impaired—whether by receptor blockade, presynaptic depletion, or neurochemical imbalance—the inhibitory control is lost, leading to excessive muscle contraction and dystonia[16]. While most EPS cases are associated with dopamine receptor antagonists, such as typical antipsychotics, a growing body of literature highlights that drugs outside the psychiatric domain can also provoke these reactions[17]. Agents such as selective serotonin reuptake inhibitors (SSRIs), calcium channel blockers, and antiemetics have been linked to acute dystonia, often through secondary dopaminergic suppression or serotonergic overactivity[18,19]. This interplay underscores the basal ganglia's vulnerability to systemic pharmacologic disturbances[20].

Risk factors for drug-induced EPS include young age, male sex, prior episodes of dystonia, and notably, metabolic disturbances such as electrolyte abnormalities and hepatic dysfunction[21,22]. In patients with compromised hepatic function, drug metabolism may be impaired, leading to higher concentrations of active metabolites capable of crossing the blood-brain barrier[23]. This is clinically paramount for drugs like metamizole, whose metabolites are predominantly hepatically processed, suggesting that patients with elevated liver enzymes or hypoalbuminemia may have increased neurotoxicity risk even with standard dosing.

In summary, despite its perceived safety and widespread use, metamizole's capacity to influence central neurotransmission warrants heightened clinical attention. The present case of hemidystonia following metamizole administration not only contributes to the limited evidence linking non-dopaminergic analgesics to extrapyramidal dysfunction but also serves to highlight the intricate challenges in pain management for medically complex patients, where polypharmacy and organ dysfunction can converge to precipitate unexpected adverse events[24].

Materials and methods

This study is a descriptive case report of a single patient who presented with an acute neurological adverse reaction. The data for this report were obtained through a detailed review of the patient's medical records, including clinical notes, laboratory results, and diagnostic imaging reports, following his admission to the Neurology Department of Dr. Soetomo General Academic Hospital.

A comprehensive diagnostic workup was undertaken to establish the etiology of the patient's acute hemidystonia. This included a full neurological and physical examination, a series of laboratory investigations, and neuroimaging. The laboratory panel consisted of a complete blood count, liver function tests, renal function tests, and serum electrolyte analysis to identify any potential metabolic triggers or comorbidities. Neuroimaging was performed using a non-contrast and contrast-enhanced computed tomography (CT) scan of the head, utilizing a standard clinical scanner, to rule out acute structural

abnormalities such as cerebrovascular events, tumors, or other intracranial lesions.

The therapeutic intervention and its response were a critical component of the clinical assessment. The patient was administered 2 ampoules (50 mg) of intravenous diphenhydramine as a diagnostic and therapeutic challenge for suspected acute drug-induced dystonia. The patient's response to this intervention was closely monitored and documented. Furthermore, a thorough pharmacological reconciliation was conducted, leading to the permanent discontinuation of the suspected offending agent, metamizole. The patient was subsequently monitored throughout his hospital stay to ensure the non-recurrence of symptoms. Informed consent was obtained from the patient for the publication of this case report, with assurances of maintaining his anonymity and confidentiality. The ethical principles of the Declaration of Helsinki were adhered to in the management of this case and the preparation of this report.

Results

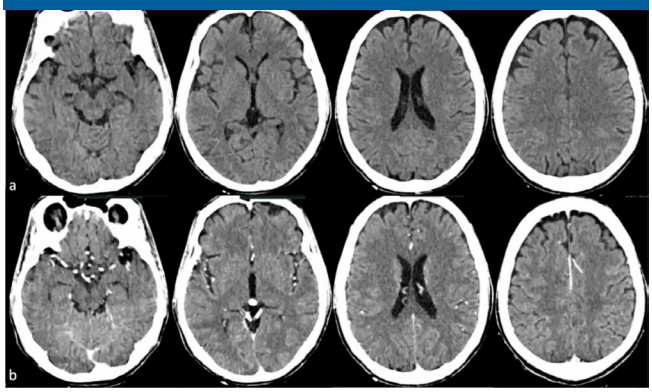
The clinical presentation, diagnostic findings, and therapeutic outcome for the patient are summarized below. The case involved a 42-year-old man who developed an acute neurological syndrome following analgesic administration.

Clinical Presentation and Timeline

A 42-year-old man was referred to the Neurology Department with sudden stiffness of the right half of his body after administration of a pain medication. This complaint was accompanied by difficulty speaking and communicating. Headache, seizure, and loss of consciousness were previously denied. The patient's family also said that the patient had a history of right half-body stiffness due to taking analgesics containing metamizole.

The patient was admitted to internal medicine with pulmonary tuberculosis accompanied by anemia, thrombocytopenia, elevated transaminase enzymes, hypoalbuminemia, hyponatremia, and hypokalemia. We also performed a head CT scan with contrast to search for any structural cause, but the CT scan was normal (Figure 1).

Figure 1. Head CT scan without contrast (a) and with contrast (b) shows normal



On examination, vital signs were found to be within normal limits. After intravenous administration of 2 ampoules of diphenhydramine, the patient's hemidystonia complaints improved. We decided to change the regimen of analgesics, and during the patient's treatment, the hemidystonia complaint did not reappear.

Systematic Clinical Findings

The patient's baseline characteristics and vital signs at the time of the neurological event are detailed in Table 1. Notably, the patient was afebrile and hemodynamically stable, ruling out an infectious or shock-related etiology for the symptoms.

Table 1: Patient Demographics and Clinical Presentation

Parameter	Finding
Age	42 years
Sex	Male
Chief Complaint	Acute right-sided hemidystonia & dysphasia
Time to Symptom Onset	Within 1 hour of metamizole injection
Past Medical History	Pulmonary Tuberculosis; Previous similar reaction to metamizole
Vital Signs	Blood Pressure: 125/80 mmHg, Heart Rate: 78 bpm, Respiratory Rate: 16/min, Temperature: 36.8°C, O2 Saturation: 98%
Consciousness	GCS 15 (Fully conscious)

A comprehensive laboratory profile, presented in Table 2, revealed a complex metabolic state. The patient presented with significant hematological abnormalities and a pattern consistent with hepatic involvement and electrolyte imbalance.

Table 2: Laboratory Investigation Profile

Test	Result	Normal Range
Hematology		
Hemoglobin	10.2 g/dL	13.5-17.5 g/dL
Hematocrit	31%	41-50%
Platelet Count	112 x 10^9/L	150-400 x 10^9/L
White Blood Cell Count	8.5 x 10^9/L	4.5-11.0 x 10^9/L
Liver Function Tests		
ALT (SGPT)	128 U/L	7-55 U/L
AST (SGOT)	110 U/L	8-48 U/L
Serum Albumin	2.9 g/dL	3.5-5.2 g/dL
Renal Function & Electrolytes		
Sodium	132 mmol/L	136-145 mmol/L
Potassium	3.2 mmol/L	3.5-5.1 mmol/L
Creatinine	0.9 mg/dL	0.7-1.3 mg/dL

The diagnostic workup, including neuroimaging, was crucial in excluding structural pathologies. The results of the primary investigations are consolidated in Table 3.

Table 3: Diagnostic Workup and Findings

Investigation	Result	Interpretation
Non-contrast Head CT Scan	No acute intracranial hemorrhage, mass effect, or territorial infarct	Normal
Contrast-enhanced Head CT Scan	No evidence of vascular malformation, tumor, or abnormal enhancement	Normal
Neurological Examination	Focal dystonia of right upper and lower limbs, involving facial muscles; Dysphasia; No sensory deficit; No cerebellar signs	Consistent with acute hemidystonia

The management and subsequent clinical course are summarized in Table 4. The rapid and targeted intervention led to a complete resolution of symptoms without recurrence.

Table 4: Therapeutic Intervention and Clinical Outcome

Parameter	Details
Suspected Agent	Metamizole (Dipyrone)
Intervention	Intravenous Diphenhydramine 50 mg (2 ampoules)
Time to Symptom Resolution	Approximately 15-20 minutes post-administration
Further Management	Permanent discontinuation of metamizole; Alternative analgesic prescribed
Follow-up Period	7 days during hospitalization
Symptom Recurrence	None

In summary, the results demonstrate a clear temporal association between intravenous metamizole administration and the acute onset of hemidystonia in a patient with significant underlying metabolic and hepatic comorbidities. The immediate and complete response to anticholinergic therapy and the absence of recurrence upon drug withdrawal strongly support a drug-induced etiology.

Discussion

Extrapyramidal syndrome (EPS) — often called extrapyramidal symptoms or extrapyramidal side effects — is an umbrella term for *drug-induced movement disorders* that result primarily from blockade or disruption of dopaminergic signalling in the basal ganglia (classically caused by D2-blocking drugs such as antipsychotics). EPS includes acute/hyperkinetic syndromes (acute dystonia, akathisia), hypokinetic syndromes (drug-induced parkinsonism), and delayed/chronic syndromes (tardive dyskinesia, tardive dystonia). Clinical features vary by subtype (e.g., rigidity/bradykinesia for Parkinsonism; inner restlessness and inability to sit still for akathisia; repetitive involuntary movements for tardive dyskinesia)[25].

A systematic review and meta-analysis of observational studies revealed that the pooled prevalence of antipsychotic-induced extrapyramidal symptoms (EPS) ranged from approximately 31% to 37%, with the prevalence decreasing from 37% before sensitivity analysis to 31% afterward. Among the specific subtypes, drug-induced parkinsonism was the most common, with a pooled prevalence of about 20%, followed by akathisia at 11%, and tardive dyskinesia (TD) at 7%. Considerable heterogeneity was observed across studies, largely attributable to variations in study settings, patient characteristics, antipsychotic drug classes, and geographical regions[25].

This case represents an exceedingly rare occurrence of metamizole-associated hemidystonia and provides insight into the broader spectrum of drug-induced extrapyramidal disorders.[1,18,24] The temporal association, recurrence upon re-exposure, and complete reversibility with diphenhydramine strongly support a pharmacologic rather than structural etiology[26].

Consistent with findings from multiple reviews, several risk factors have been identified as contributing to the development of EPS, including older age, female sex (particularly for certain EPS subtypes), higher doses of antipsychotics, and the use of agents with high dopamine D2 receptor affinity—particularly first-generation (typical) antipsychotics compared to many second-generation (atypical) agents. Longer duration of antipsychotic exposure, history of acute EPS, comorbid neurological conditions, and pharmacologic interactions have also been implicated in increasing susceptibility[27]. Given the significant impact of EPS on treatment adherence and quality of life, vigilant monitoring, early detection, and timely management remain crucial in minimizing morbidity associated with these adverse effects[27]. In our case, this patient also had a history of acute EPS caused by metamizole.

The basal ganglia are central to the pathogenesis of dystonia, coordinating sensory input and motor output through two major pathways: the direct (facilitatory) and indirect (inhibitory) motor circuit[15]. These pathways are modulated by dopaminergic neurons from the substantia nigra pars compacta. Drug-induced dystonia often occurs when dopaminergic transmission is disrupted, leading to overactivity of cholinergic interneurons in the striatum. The resulting disinhibition of thalamocortical projections manifests as sustained or repetitive muscle contractions[16,28].

Although metamizole does not act as a dopamine receptor antagonist, several indirect mechanisms could contribute to dopaminergic dysfunction. First, animal studies have shown that its active metabolite, 4-MAA, can decrease dopamine turnover in the nigrostriatal pathway[29]. Second, metamizole's modulation of serotonin and GABA systems may suppress dopaminergic tone via serotonergic inhibition or altered inhibitory feedback.[19] Third, systemic metabolic stress—such as hyponatremia, hypokalemia, or hepatic impairment—can potentiate neuronal excitability, increasing susceptibility to dystonic reactions even without direct receptor blockade[21].

Comparatively, SSRIs, valproate, and certain antiepileptics have also been reported to induce dystonia through non-dopaminergic mechanisms[18,30]. For instance, SSRIs elevate serotonin levels that inhibit dopamine release in the basal ganglia, while valproate alters GABAergic transmission and mitochondrial energy metabolism[31]. These examples underscore the multifactorial basis of drug-induced dystonia, in which several neurotransmitter systems intersect to disrupt basal ganglia homeostasis[20]. Although metamizole was never reported as one of the causal drugs of EPS.

An intriguing aspect of this case is the unilateral (hemidystonic) manifestation, which is uncommon in drug-induced EPS. Functional imaging studies have suggested that asymmetrical distribution of dopaminergic receptors or regional variations in cerebral perfusion may produce lateralized symptoms[31]. This patient's previous exposure to metamizole and recurrence on re-exposure may also suggest a kind of "sensitization phenomenon," in which prior dopaminergic disturbance primes neural circuits for exaggerated response to subsequent triggers[32].

Another critical element involves pharmacogenomics. Polymorphisms in dopamine receptors (DRD2, DRD3) and drug-metabolizing enzymes such as CYP2C19 and NAT2 can alter individual susceptibility to EPS[28,34]. Slow metabolizers of pyrazolone derivatives may accumulate higher levels of 4-MAA, leading to prolonged exposure of dopaminergic neurons to neuroactive metabolites[26]. Similarly, hepatic dysfunction and low albumin levels, as seen in this patient, can increase the free fraction of these metabolites, amplifying neurotoxicity risk[22].

Management of neuroleptic-induced acute dystonia requires prompt pharmacologic intervention to relieve symptoms and prevent recurrence. First-line therapy involves the administration of diphenhydramine, which has a high level of evidence (LOE: high), or the use of anticholinergic agents such as benztropine or biperiden (LOE: very low). Patients and their families should be advised that, in the event of an acute dystonic reaction, an oral dose of diphenhydramine can be self-administered while seeking medical care.

Symptoms typically resolve within minutes following parenteral therapy; however, repeat dosing may be necessary if no improvement occurs within 30 minutes. Intravenous diazepam, supported by high-level evidence, may serve as an alternative treatment option in refractory cases. To prevent recurrence, short-term continuation of therapy for two to five days may be warranted. If ongoing antipsychotic therapy is essential, clinicians should consider lowering the antipsychotic dose or co-administering an anticholinergic agent (LOE: high) to mitigate further dystonic reactions[36].

From a therapeutic standpoint, the immediate response to diphenhydramine highlights the central role of cholinergic imbalance.[17] Diphenhydramine exerts both antihistaminic and anticholinergic effects, restoring dopaminergic-cholinergic equilibrium within the basal ganglia. The absence of recurrence following metamizole withdrawal reinforces the reversible, non-degenerative nature of this adverse event[17].

Clinicians should exercise caution when prescribing metamizole, particularly in patients with predisposing metabolic or hepatic conditions[37]. Documentation of prior adverse drug reactions is essential to avoid re-exposure. Furthermore, collaboration with pharmacovigilance programs should be encouraged to improve reporting accuracy for such rare events[1]. A heightened awareness among healthcare professionals can prevent misdiagnosis of drug-induced dystonia as cerebrovascular accident, seizure, or functional neurological disorder[38].

The resolution of symptoms following administration of diphenhydramine - an antihistamine with anticholinergic properties - further supports a diagnosis of acute dystonia, as anticholinergics are known to be effective in reversing this condition. Importantly, discontinuation of metamizole and substitution with an alternative analgesic prevented recurrence, reinforcing the drug's probable role in symptom genesis.

From a diagnostic perspective, this case also illustrates the importance of excluding structural or metabolic causes of focal neurological symptoms. The patient's stable vital signs and normal sensorium, combined with the rapid response to pharmacologic intervention, argued against an acute cerebrovascular event or infection.

Finally, future research should aim to delineate the neurochemical pathways through controlled neuroimaging studies and animal experiments[39]. Elucidating the mo-

lecular interactions between metamizole metabolites and dopaminergic or serotonergic systems could advance our understanding of non-traditional causes of extrapyramidal disorders.[40] Expanding pharmacogenomic screening and monitoring strategies may also help identify high-risk individuals[41].

Conclusions

This case report presents a rare but significant instance of acute hemidystonia unequivocally linked to the administration of metamizole. The strong temporal relationship, the striking recurrence upon re-exposure, and the immediate resolution following anticholinergic intervention collectively provide a compelling argument for a drug-induced etiology. Furthermore, the patient's unique clinical backdrop—characterized by hepatic impairment, electrolyte imbalances, and hypoalbuminemia—highlights the critical role of individual metabolic status in predisposing patients to such adverse neurological reactions. This suggests that the neurotoxicity of metamizole's active metabolites is not merely a rare idiosyncrasy but can be potentiated by specific, identifiable patient factors. From a clinical management perspective, this case underscores the efficacy of a structured approach. The prompt administration of diphenhydramine served both as a diagnostic tool and a therapeutic remedy, leading to the rapid alleviation of symptoms. The definitive preventive measure—the permanent discontinuation of the offending agent—proved entirely successful, as no recurrence was observed during follow-up. This successful outcome reinforces established management protocols for acute drug-induced dystonia and demonstrates the importance of a thorough pharmacological reconciliation in patients presenting with acute movement disorders.

In conclusion, while metamizole remains a valuable analgesic in many contexts, this report expands the known spectrum of its potential neurological adverse effects. It serves as a critical reminder to clinicians that vigilance should extend beyond a drug's most publicized risks. A heightened index of suspicion for extrapyramidal syndromes is warranted, particularly in medically complex patients with compromised metabolic or hepatic function. Ultimately, this case champions the principles of pharmacovigilance and personalized medicine, advocating for a cautious and informed approach to analgesic selection to ensure patient safety.

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