

Wrong-route drug administration errors: A review of the literature

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Oral drug formulations and enteral feeds may inadvertently be administered intravenously. Intravenous medications may be inadvertently administered intra-arterially. These examples of wrong-route drug administration errors have the potential to cause significant organ dysfunction and even death. This narrative review aims to explore the pathophysiological mechanisms underlying such errors and investigate preventive strategies and potential therapeutic options.

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The administration of an oral drug via the intravenous route is classified as a wrong-route drug administration error.^[1,2] These errors, associated with high risk of morbidity and mortality, are grossly under-reported and under-recognised.^[3] The National Poisons Center of Ireland reported that 5% of medication errors occurring between January and December 2009 were related to wrong-route errors.^[4] In 2021, a study examining medication errors in public hospitals reported only 6 of 315 medication errors to be related to wrong-route administration in Gauteng, South Africa (SA).^[5] In email communication with Dr Cindy Stephen (July 2022), an estimated 5 such cases are reported to the Poisons Centre in Cape Town, SA, annually.

The four most common clinical scenarios related to wrong-route administration are the inadvertent administration of oral drug formulations intravenously, the inadvertent administration of enteral feeds intravenously, the inadvertent intra-arterial administration of intravenous medications and the intentional intravenous administration of crushed tablets by intravenous drug users (IVDUs).

Complications related to these errors include sepsis from the injection of unsterile solution, and embolic complications from insoluble particulate matter, high-viscosity solutions and fat globules.^[6,7] Talc, microcrystalline cellulose (MCC), crospovidone and starch are common insoluble substances found in oral drug formulations that are reported to embolise and induce granulomatous reactions.^[6-9] Emboli may cause cardiovascular and respiratory collapse, and multi-organ failure. Disseminated intravascular coagulation (DIC), anaphylactic or hypersensitivity reactions to foreign antigens and phlebitis related to high osmolality solutions have also been reported.^[1,2,10-12] Characteristics of the incorrectly administered infusate, such as the composition (enteral feed v. medication), size of particulate matter, volume administered and rate of administration are hypothesised to predict the resulting clinical severity.^[10,13] Finally, oral drugs administered intravenously may have greater drug bioavailability with potential for toxicity.^[14]

Inadvertent intravenous administration of oral drug formulations

In one case report, a 74-year-old female was given verapamil oral solution and diclofenac dispersible tablets via a central venous catheter. She rapidly deteriorated, with respiratory arrest, hypoxia and coma.^[3]

After resuscitation, she underwent further special investigations. Both echocardiography and computed tomography (CT) of the brain were unremarkable. CT pulmonary angiogram (CTPA) demonstrated no vascular filling defects, but bilateral pleural effusions. Within 2 hours of collapse her oxygen saturation had improved to 99%, and she was extubated 1 day later. Her clinical course was further complicated by the development of methicillin-resistant *Staphylococcus aureus* sepsis requiring re-intubation, ventilation and tracheostomy. She was eventually discharged. It is postulated that her ventilation-perfusion mismatch and hypoxic respiratory arrest was related to pulmonary circulation microemboli from insoluble excipient particulates in oral preparations. MCC and talc were implicated as being the most likely and dangerous culprits.^[3]

MCC, an excipient commonly found in oral drug formulations, is inactive and functions as a binding agent.^[6,15] Insoluble MCC injected intravenously becomes trapped in pulmonary arterioles and can induce granulomatous inflammation.^[6] Embolisation of MCC to the pulmonary vasculature has been reported in association with the intentional injection of crushed oral tablets in IVDUs, and inadvertent wrong-route administration of oral treatments.^[15] Presentation may be acute, with collapse and dyspnoea related to arterial occlusion with pulmonary hypertension, cor pulmonale and cardiac arrest. More gradual onset of progressive dyspnoea from extensive pulmonary granulomatosis is reported in IVDUs.^[15] As compared with MCC, smaller talc particles may pass through the pulmonary vasculature and lodge in distant organs, such as the liver or spleen, inciting inflammatory reactions. Intravenous talc injection is also associated with acute onset of adult respiratory distress syndrome (ARDS).^[9] Starch induces less of a foreign body immune reaction than MCC, but can still be responsible for significant vascular occlusion if administered in large volumes.^[9] Crospovidone, another common excipient, has also been shown to induce acute thrombosis and granulomatous reactions in the pulmonary vasculature.^[8]

El Mazloum *et al.*^[11] report the inadvertent administration of 6 mL paracetamol syrup intravenously in an 18-month-old child. Some paracetamol syrup formulations are reported to contain MCC as an excipient.^[16] The child was admitted to the ICU for monitoring as a precautionary measure, but remained asymptomatic. Doppler ultrasound of the accessed vein did not reveal thrombosis. Echocardiography was normal. Bacterial culture of remaining paracetamol syrup revealed no growth, and the child was subsequently discharged.^[11]

Kwon *et al.*^[6] report the case of a 32-year-old female requiring total parenteral nutrition via a peripherally inserted central catheter (PICC) for short-bowel syndrome, and with comorbid factitious disorder. While admitted, she acutely developed chest pain, dyspnoea, hypotension and hypoxia. Echocardiogram showed new severe right ventricular dilatation with dysfunction. The patient later died. Autopsy confirmed her cardiac arrest was related to pulmonary MCC emboli with extensive granulomatosis. Intentional administration of oral medications via PICC line was suspected.

Inadvertent intravenous administration of enteral feeds

Administering enteral feeds intravenously is associated with risk of bacterial contamination. Cases reported in the literature often present with shock and pyrexia.^[17,18] Inflammatory and hypersensitivity reactions to the protein components of feeds, osmolality-related thrombophlebitis and fat embolism are additional concerns.^[17] Simmons *et al.*^[19] reported 21 deaths in 116 case reports of intravenous administration of enteral feeds between 1972 and 2010.

Ramsay *et al.*^[17] report the case of a 41-year-old male IVDU requiring mitral valve replacement. Post discharge from the ICU he inadvertently received 300 mL enteral feed via central venous catheter. He deteriorated with the development of hypotension, hypoxia, pyrexia and bilateral crackles on auscultation. He required ventilatory and inotropic support and his clinical course was complicated by DIC. Echocardiography excluded new valve vegetations. The enteral feed and patient's blood sample were sent for bacterial culture. Both cultures flagged positive for multiple bacteria and imipenem, netilmicin and vancomycin were initiated. He was successfully discharged weeks later.^[17]

Doring *et al.*^[13] report the inadvertent intravenous administration of 5 mL of expressed breast milk to a 49-day-old infant with subsequent sudden-onset hypoxia, tachypnoea and tachycardia. Chest radiography, echocardiography and electrocardiogram were unremarkable. Antibiotic therapy with ampicillin was commenced, and subsequently stopped 48 hours later as cultures of expressed milk were negative for bacterial growth. The child's tachypnea, tachycardia and hypoxia rapidly improved, with discharge from ICU 24 hours post incident.

Sen *et al.*^[20] described the case of a 60-year-old female who inadvertently received 25 mL of enteral feed via central IV line. She developed chills, tachypnoea, tachycardia and hypotension. The central line was removed. She required resuscitation in ICU and treatment with intravenous antihistamines, dobutamine, noradrenaline, vasopressin, hydrocortisone and prophylactic doses of unfractionated heparin. Blood samples sent for bacterial culture grew *Klebsiella* species, and piperacillin/tazobactam was initiated. Her haemodynamic instability improved, and eventually she was discharged.

Management

Historically, management of wrong-route drug errors has included supportive care and is based largely on case reports.^[6,12,17] Early recognition of this complication should be followed by immediate cessation of the infusion and removal of the line. Patients presenting with acute deterioration may require resuscitation with intubation, ventilation, intravenous fluids and inotropic support. Asymptomatic patients should continue to be monitored in a high care setting for ongoing deterioration. Specimens of the oral drug or enteral feed, and from the patient, should be collected for bacterial culture. Empirical initiation of broad-spectrum antibiotics based on local antimicrobial resistance patterns is recommended. Antibiotic therapy

may later be stopped, or tailored to the results of blood and infusate cultures. Appropriate special investigations are advised to detect deteriorating organ function and DIC. CTPA, echocardiography and Doppler ultrasound can exclude differential diagnoses and assess for complications. Prophylactic doses of anticoagulants are advised to prevent further clot propagation. Discharge of patients remaining asymptomatic 24 hours after the event may be considered. Additionally, in line with the National Guideline for Patient Safety Incident Reporting and Learning in the Health Sector of SA,^[21] and professional and ethical obligation, healthcare workers should disclose the incident to the patient or next of kin.^[22,23]

Two case reports have referenced the use of plasmapheresis and exchange transfusion in enteral feed-associated wrong-route errors.^[24,25] Ong *et al.*^[24] report the case of a 50-year-old male with oesophageal carcinoma who received 100 mL of enteral feed via peripheral intravenous line. He presented with tachycardia, hypotension, dyspnoea and fever. He required extensive resuscitation and empirical intravenous antibiotics. Samples of the enteral feed and blood culture flagged positive for *Klebsiella* species. To remove foreign antigens, lipid particles and bacterial endotoxins, the patient underwent two cycles of plasmapheresis. After the first cycle, a significant improvement in condition allowed for weaning of inotropes, and after 24 hours, he was weaned from ventilatory support.

At present, only low-quality evidence exists for the use of aphaeresis for similar indications. According to the American Society of Apheresis, the optimum role of aphaeresis in sepsis, drug overdose or poisoning is not established, and decision-making should be individualised.^[26]

Prevention

Prevention of wrong-route administration errors remains paramount. The WHO Collaborating Centre on Patient Safety Solution's Joint Commission has highlighted factors contributing to these types of errors, and makes recommendations for prevention.^[27] The widespread use of Luer locks in medical settings problematically allows for the connection of dissimilar tubes (such as enteral and intravenous tubing).^[14] Ideally, only catheters and tubing that are incompatible by design should be procured.^[28] Luer-connection intravenous syringes should not be used to administer oral medications or enteric feeds.^[3] Rather, only oral syringes that are incompatible with venous catheters should be used to prepare and administer oral medications.^[2,3] Use of tubing for purposes other than intended, such as line extensions, also predisposes to wrong-route errors.^[27] Connections between tubing, catheters and devices should never be forced. Any connection that cannot be made easily or requires a makeshift adaptor should alert the healthcare practitioner that something is amiss. Risk of wrong-route errors is further increased when intravenous and enteral feeding tubing is intertwined, also known as the 'spaghetti syndrome'.^[13,27] Consider directing lines in alternate directions, for example, intravenous lines towards the head and enteral feeding lines towards the feet of the patient.^[27] All lines and tubing should be traced from their point of origin to the proposed connection point prior to making connections.^[13] Furthermore, catheters, tubing and syringes should always be labelled.^[3,14]

Insufficient supervision of junior staff and a lack of knowledge or experience have also been cited as risk factors for drug administration errors. Staff should be educated on the dangers of wrong-route errors and trained on how to prevent them. Staff fatigue from long hours and consecutive shifts also increases the risk of error.^[2,27] In a randomised, rater-blinded study conducted by Landrigan *et al.*,^[29] medical interns

working extended shifts of >24 hours (approximately 77 - 81 hours per work week) made 20.8% more serious medication errors than when working shifts limited to 16 consecutive hours (approximately 60 - 63 hours per week). Additionally, environmental factors such as poor lighting, and distractions that result in loss of situational awareness, must be avoided.^[2] The person preparing a medication should always be the one to administer it. Delays between preparing the drug, confirming the identity of the patient and administration of the drug should be minimised.^[11,19] Finally, preventive measures should include educating patients, family members and non-clinical staff to never disconnect or connect lines themselves.^[13,28]

Inadvertent intra-arterial administration: A special situation

The inadvertent intra-arterial administration of intravenous or oral formulations is associated with significant morbidity. Early recognition and management are essential to prevent the loss of limb.^[30] Historically, this error has predominantly occurred during anaesthesia, with the earliest reported culprit drugs barbiturates and benzodiazepines.^[18] Subsequently, case reports have implicated a variety of agents, including penicillin, phenytoin, promethazine, dextrose-containing intravenous fluids and sodium bicarbonate.^[18,31-33] More recently, complications of inadvertent intra-arterial administration of drugs of abuse are being recognised in IVDUs.^[18,33]

The antecubital fossa of the upper limb, where the radial and brachial arteries lie near the cephalic and basilic veins, is particularly high risk.^[33] When iatrogenic, this complication is usually rapidly recognised, as patients report pain on injection, followed by weakness and paraesthesia distal to the injection site.^[18] On examination, oedema, cyanosis, flushing or mottling of the skin, reduced temperature of the limb and delayed capillary refill may be noted.^[34] Between 48 hours and 14 days post injury, functional deficits, compartment syndrome, skin and digital necrosis and gangrene with auto-amputation may develop.^[18,30] Doppler ultrasonography, ankle-brachial index measurements and angiography assist in confirming the diagnosis and assessing the severity of injury.^[35,36]

Multiple pathophysiological mechanisms underlie the injury sustained from intra-arterial injection, which culminate in reduced tissue perfusion and ischaemia distal to the injection site. Drugs may induce inflammation of the arterial endothelium, a so-called 'chemical endarteritis', and be directly cytotoxic to endothelial cells.^[35] Noradrenaline-mediated vasospasm, thromboxane release with platelet aggregation and thrombus formation also contribute to reduced tissue perfusion.^[18] Furthermore, it has been proposed that some drugs may precipitate crystals at the pH of arterial blood that block downstream arterioles.^[18,30,35] Not all drugs administered intra-arterially are associated with local ischaemic damage. It is hypothesised that the risk associated with an agent is related in part to its lipid solubility. Highly lipid-soluble drugs can traverse the endothelial cell membrane, inducing lysis of cells and denuding the endothelial lining of the vessel, with eventual thrombosis.^[31,36] Increasing volume, concentration and osmolality of agents injected increases the risk of local damage.^[33]

The lack of robust evidence comparing treatment modalities makes management recommendations for this type of injury challenging. Therapeutic interventions referenced in the literature are based on evidence from animal studies, case reports or cohort studies involving IVDUs, who tend to present with more advanced and severe disease.^[30,36] Five main clinical end-points to direct management of inadvertent intra-arterial drug administration are proposed, namely: symptomatic relief of pain, reversal of arterial

spasm, re-establishing perfusion to the distal extremity, treatment of ischaemic complications and rehabilitation to restore function.^[18]

Aggressive use of analgesia is advised, to reduce the increase in sympathetic vascular tone that results from pain.^[18] Slight elevation of the affected limb allows for an improvement in oedema and contributes to relief of pain.^[18,30,35,37] In iatrogenic cases of intra-arterial injection, it is recommended to maintain the intra-arterial catheter, rather than remove it, to allow for the direct administration of medications to the site of injury.^[18]

The most widely recommended aspect of treatment is the initiation of unfractionated heparin to prevent extension of thrombosis. An initial loading dose of 5 000 IU heparin, followed by continuous infusion to maintain the partial thromboplastin time two times the control value has been recommended.^[18,30,37] Ongoing heparin infusion, until resolution of pain and swelling or angiographic improvement, is advised.

A wide variety of additional treatment modalities are discussed in case reports, including aspirin, clopidogrel, local anaesthetics, corticosteroids, calcium channel blockers, reserpine, papaverine and prostaglandins.^[33,37,38] Aspirin and clopidogrel have been used for their anti-platelet activity.^[37] Intra-arterial injection of local anaesthetic to relieve both pain and vasospasm has been reported.^[37] Blockage of sympathetic outflow to the affected limb via stellate ganglion or brachial plexus block produces vasodilation and has been used to relieve pain and improve perfusion. However, because of the risks associated with this intervention, particularly in the context of concomitant anticoagulation, it is not considered a first-line intervention.^[18,35,37] The use of corticosteroids to reduce endothelial inflammation has also been reported.^[18] Aspirin and methylprednisolone provide the additional benefit of also inhibiting thromboxane.^[18] Prostaglandin E1 and E2 (prostanolol), indicated in the management of refractory Raynaud's phenomenon, have also been used for their vasodilatory effect and anti-platelet effects.^[18,30,33]

Lysis of formed thrombus via catheter-directed intra-arterial use of thrombolytics, such as urokinase and tissue plasminogen activator (tPA), may result in successful restoration of perfusion.^[30,37] The use of thrombectomy to restore perfusion in larger-vessel thrombosis has also been reported.^[18,35] Surgical intervention is predominantly directed at the management of ischaemic complications, and involves amputation or debridement of gangrene. Finally, hyperbaric oxygen therapy, which increases the partial pressure of oxygen in tissues, may also play a role in the management of these injuries.^[18,36]

The prevention of iatrogenic intra-arterial drug administration involves identifying high-risk situations and applying extra caution. For example, recognition of this injury can be delayed in sedated or anaesthetised patients. Extra caution should be taken when obtaining intravenous access in high-risk areas. Additionally, in patients with difficult venous access, where available, the use of ultrasound may assist in achieving and confirming correct venous placement.^[39] Common signs of inadvertent intra-arterial catheterisation must be recognised, such as the back flow of bright red blood and a pulsation of blood in tubing. Furthermore, preventing arterial line connection errors is essential. Educating healthcare professionals and IVDUs regarding the risks, signs, symptoms and complications associated with unintentional intra-arterial injection is paramount to prevention.^[18]

Conclusion

In conclusion, wrong-route drug administration errors have the potential to cause significant organ dysfunction and even death. Prevention, recognition and reporting of these errors should be prioritised. The use of anticoagulation and broad-spectrum antibiotics

is widely agreed upon. However, the lack of robust evidence relating to other therapeutic interventions means that blanket recommendations are inappropriate, and until such time as further research becomes available, an individualised approach is advised.

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