

An ultra-rapid development of tachyphylaxis to nitroglycerin

Sir,

A 30-year-old man, weighing 56 kg, with no co-existing illness, was posted for endoscopic excision of left sided nasopharyngeal angiofibroma. His laboratory parameters were normal, pulse rate was 86 beats/min and blood pressure (BP) was 130/80 mmHg during the pre-anaesthetic evaluation. Hypotensive anaesthesia was planned in anticipation of excessive blood loss.

After initiating routine monitoring, and invasive BP via the left radial artery, general anaesthesia was induced with fentanyl and propofol. Neuromuscular blockade was achieved with vecuronium and airway secured with an endotracheal tube. Anaesthesia was maintained with propofol infusion, nitrous oxide in 30% oxygen, and controlled ventilation. Nitroglycerin (glyceryl trinitrate [GTN]) infusion was started at 10 µg/min. There was an increase in pulse rate from 65 to 72 beats/min and minimal change in BP. Anticipating tachycardia, intravenous metoprolol 4 mg was given, which reduced the heart rate to pre-GTN level. Since, the BP did not reach the desired level, we escalated GTN infusion over the next 5 min which had no effect. Analgesia, intravascular volume and patient position were deemed adequate. Suspecting problem with potency of the drug, GTN from two different manufacturers (maintained in cold chain) were tried without any success. GTN was tried even in 5 mg boluses and we ended up using 75 mg

of GTN in a span of 15 min. The nasal cavity was packed with adrenaline-soaked gauze before surgery. But adrenaline was not used intra-operatively by the surgeon.

We thought of other conditions like paraganglioma, adrenal pheochromocytoma, and alerted the surgeon. However, the surgeon was confident of the nature of the tumour because of the intra-operative findings. We were contemplating to use sodium nitroprusside. However, the surgeon was satisfied with the surgical field and able to manage without induced hypotension. Total blood loss was 450 ml. Urine sample for metanephrines and vanillylmandelic acid ruled out pheochromocytoma/paraganglioma and histopathology report confirmed angiofibroma.

Anaesthetics agents and many pharmacological agents are used either alone or in combination to achieve the haemodynamic goals during hypotensive anaesthesia.^[1] Intravenous GTN is commonly used in the perioperative setting for acute control of hypertension, treat angina, and provide hypotension because of its easy administration, rapid onset of action, easy titrability, rapid termination of action after stopping the infusion, rapid elimination without toxic metabolites, and very few side effects.

Glyceryl trinitrate is very widely used in the acute management of angina. However, the chronic efficacy of nitrates is blunted because of the development of tolerance. Known since the first clinical use of nitrates,^[2] the problem of tolerance is a complex phenomenon involving neurohormonal counter-regulation (known as pseudotolerance) as well as intrinsic vascular tolerance. Neurohormonal mechanisms involved in pseudotolerance are not specific to GTN and have been observed with other vasodilators. GTN-induced desensitization of vasodilator responses to nitric oxide (NO) donors and endothelium-derived NO is termed cross-tolerance. An acute loss of GTN efficacy at intermediate to high concentrations in *in-vitro* experiments is called tachyphylaxis.^[2] Multiple theories have been proposed to explain the mechanism of true tolerance; (1) Impaired nitrate bioconversion resulting in diminished NO release^[3] and (2) increased NO clearance mediated by the generation of superoxide (O₂⁻).^[4]

Our suspicion of an inactive/less potent GTN was ruled out by trying the drug manufactured by three different manufacturers. Our concerns were of a

nasopharyngeal paraganglioma, an extremely rare tumour with unpredictable biological behaviour,^[5,6] which could pose a threat to patient's life because of the potential to release catecholamines. The points against were absence of a history of paroxysmal hypertension, headache, sweating, and palpitation, no fluctuation of BP peri-operatively, and the intra-operative surgical findings.

Very minimal and short lived hypotensive response to GTN shown by this patient was probably because of the hyper-acute development of tachyphylaxis. We are not aware of any literature reporting such a rapid development of tachyphylaxis to GTN and such high doses being used without any effect. Clinicians, especially in the perioperative setting, should have additional plans consisting of different drugs to achieve their haemodynamic goals because of the minimal time available, and the need for rapid and tight control of BP.

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Quick response code	Website: www.ijaweb.org
	DOI: 10.4103/0019-5049.147183