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Anesthesia increases circulating glutamate in neurosurgical patients

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Summary

Background. The excitotoxic amino acid glutamate is known to aggravate pre-existing neuropathology. Since volatile anesthetics increase plasma amino acid levels, we investigated if the anesthetics isoflurane and propofol increase plasma and cerebrospinal fluid (CSF) glutamate in neurosurgical patients.

Methods. In discectomized patients ($n = 15$), plasma glutamate was determined at 30 minute intervals before and during isoflurane anesthesia. In craniotomized patients ($n = 66$), plasma glutamate was assessed during and up to 24 hours after routine isoflurane or propofol anesthesia. CSF samples were withdrawn upon opening of the dura, before surgical manipulations.

Findings. During isoflurane anesthesia, plasma glutamate was significantly and reversibly increased in discectomized and craniotomized patients compared to healthy controls ($56 \pm 6\,\mu M$; $p < 0.05$), which was mostly sustained in male patients (males: 126 ± 12 vs. females: $96 \pm 6\,\mu M$; $p < 0.05$). With propofol, plasma glutamate was increased equally in men and women but to a lesser extent than with isoflurane (mean: $72 \pm 7\,\mu M$). CSF glutamate was significantly increased during isoflurane and propofol anesthesia compared to control lumbar CSF ($1.2 \pm 0.1\,\mu M$; $p < 0.0001$), being more prominent in patients with pre-existing brain edema receiving isoflurane (76 ± 8 vs. propofol: $40 \pm 6\,\mu M$; $p < 0.05$).

Conclusions. The significant increases in plasma and CSF glutamate which were mostly sustained during isoflurane compared to propofol anesthesia should prompt the identification of anesthetic agents which do not impose a possible burden of glutamate-mediated excitotoxicity in patients with underlying compromised cerebral homeostasis. Detailed neuropsychological investigations following different anesthesia regimen are important to determine if transient elevations in CSF and plasma glutamate levels are of clinical relevance.

Keywords: Amino acids; high performance liquid chromatography; injectable anesthetics; isoflurane; propofol; volatile anesthetics.

Introduction

Within the mammalian central nervous system (CNS) glutamate is the most abundant excitatory neurotransmitter amino acid [12]. Apart from its physiological role in neuronal excitation glutamate is also known to cause structural and functional damage including cellular swelling and neuronal death [29]. Tightly regulated and energy-dependent uptake mechanisms for glutamate are required to maintain low extracellular glutamate levels and to prevent excessive neuronal activation and cell death [29, 8]. Under physiological conditions free passage of plasma glutamate is inhibited by the intact blood-brain barrier (BBB) as cerebral endothelial cells possess important anatomical features, saturable carrier systems and enzymes known to regulate the access of amino acids to the CNS [30]. Experimental studies in healthy volunteers and animals have shown that release of glutamate from the brain as reflected by a negative arterio-jugular venous difference outweighs the extraction from arterial blood [19, 10]. These findings show that the uninjured brain successfully prevents uncontrolled influx of potentially toxic plasma glutamate concentrations. Under pathological conditions, however, plasma glutamate levels have been shown to passively follow their gradient, traversing the damaged BBB, flooding the cerebral extracellular space [21] and aggravating underlying brain edema [20, 41]. Administration of selective glutamate-receptor antagonists prevented evolving tissue damage [41] which underlines the importance of plasma glutamate within the pathophysiology of vasogenic and cytotoxic brain edema formation.

In addition to the underlying neuropathology, neurosurgical interventions can cause local tissue and BBB damage related to employed retractor pressure [34]. This, in turn, could increase the susceptibility of

the already compromised brain to glutamate-mediated toxicity.

Volatile anesthetics reversibly elevate plasma concentrations of essential and non-essential amino acids in humans and dogs [5, 17, 18]. These investigations, however, did not specifically address changes in plasma and cerebrospinal fluid (CSF) glutamate. Thus, we investigated the influence of the routinely used volatile anesthetic isoflurane (Forane®) and injectable anesthetic propofol (Diprivan®) on plasma and CSF glutamate concentrations in neurosurgical patients, subjected to elective discectomy and craniotomy.

Materials and methods

Only patients free of clinical and chemical signs of hepatic, renal, and metabolic dysfunction were included in this open, prospective, and descriptive clinical study. The electively surgically treated patients were subject to overnight fasting as part of routine pre-surgical preparation. Choice as well as dosage of employed anesthetics were not influenced by the investigators. The present study was approved by the local Ethics committee.

Anesthesia

Balanced anesthesia was performed with the volatile anesthetic isoflurane (Forane®). Anesthesia was induced by intravenous injection of thiopental (Pentothal®) (3–5 mg/kg), fentanyl (0.03 mg/kg), and pancuronium (0.1 mg/kg). Anesthesia was then maintained with a mixture of isoflurane (0.6–0.8 vol%), nitrous oxide and oxygen (60 vol%: 40 vol%) combined with continuously infused fentanyl (0.05–0.1 mg/kg/h). Total intravenous anesthesia was induced and maintained with propofol (Diprivan®) and alfentanyl [induction: 2 mg/kg propofol and 0.03 mg/kg alfentanyl; maintenance: continuous infusion of 3–5 mg/kg/h propofol and 0.05 mg/kg/h alfentanyl].

Blood and CSF sampling

Initial blood samples (0.5 ml) collected with commercially available heparinized syringes to determine arterial blood gases were taken approximately 30 minutes before induction of anesthesia. In electively discectomized patients blood samples were withdrawn at 30 minute intervals during anesthesia using isoflurane. In craniotomized patients subjected to elective surgical tumor removal, plasma samples were drawn every hour during isoflurane and propofol anesthesia, followed by sampling directly upon arrival on the neurosurgical intensive care unit and 12 hours after termination of anesthesia.

At approximately 2 hours after induction of anesthesia, i.e., immediately upon opening of the dura mater and before any neurosurgical manipulation of the brain, subarachnoid CSF samples (1 ml) were drawn. Only CSF samples macroscopically free of blood were analyzed.

Control plasma and CSF values

Venous plasma samples were drawn from 20 healthy individuals at 08:00 a.m. after an overnight fast. Control CSF was taken from 20 non-injured patients following diagnostic lumbar puncture presenting with headache and lumbar back pain of unclear etiology. Lumbar punctures in these patients were performed to exclude subarachnoid hermorrhage and infections as previously described in more detail [36].

Blood brain barrier damage

Presence of vasogenic edema was evaluated by neuroradiologists based on the extravasation of contrast medium in CT scans and MR images independently of the present study. To determine a potential passive increase in CSF glutamate related to an underlying damaged BBB, the CSF to plasma glutamate ratio was calculated by dividing CSF with corresponding plasma levels. In addition, influence of plasma on CSF glutamate for each individual patient was determined by linear regression analysis.

Glutamate analysis and dilution with Diprivan®

Glutamate was analyzed by high performance liquid chromatography using ortho-phthaldialdehyd pre-column derivatisation and fluorescence detection as previously described [36]. To exclude an artifical decrease in plasma glutamate related to physicochemical interference of the opaque drug Diprivan® and possible hindered binding of ortho-phthaldialdehyd, we diluted plasma samples obtained from 3 controls with Diprivan® or saline solution by 0, 25, 50, and 75%. These measurements were performed in duplicate.

Statistical analysis

Glutamate concentrations and clinical parameters are presented as mean ± SEM using the statistical analysis programme SigmaStat® 2.0. Investigated parameters were compared for significant differences over time (plasma glutamate) and between the different groups (CSF, CSF to plasma glutamate ratio) using analysis of variances (ANOVA) on ranks followed by post hoc multiple comparisons. P values are presented following correction for multiple comparisons. Mutual dependencies between CSF and plasma glutamate were determined by linear regression analysis. Differences were rated significant at $p < 0.05$.

Results

Patient characteristics

A total of 15 patients (6 female and 9 male) were electively discectomized, all of whom were anesthetized with isoflurane (Forane®). Age (female: 42 ± 4 vs. male: 39 ± 5 years), duration of anesthesia (124 ± 14 vs. 138 ± 19 minutes) and surgery (188 ± 23 vs. 156 ± 13 minutes) were similar in male and female patients.

A total of 66 patients were electively craniotomized for tumor removal, of whom 15 female and 15 male patients ($n = 30$) received isoflurane (Forane®) and 17 female and 19 male patients ($n = 36$) were given propofol (Diprivan®), respectively. Age (isoflurane: 46 ± 3 vs. propofol: 36 ± 2 years), length of anesthesia (342 ± 24 vs. 338 ± 21 minutes) and surgery (238 ± 26 vs. 236 ± 20 minutes) were similar in both anesthesia groups.

Plasma glutamate levels

In healthy controls, plasma glutamate levels were similar in female ($46 \pm 10\,\mu M$) and male ($57 \pm 7\,\mu M$) volunteers. Within 30 minutes after induction of anesthesia with

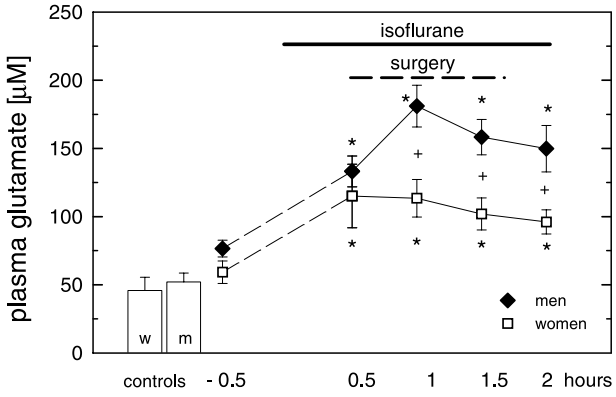

Fig. 1. Plasma glutamate was significantly increased in electively discectomized female ($n = 6$) and male ($n = 9$) patients receiving isoflurane compared to pre-anesthesia levels and healthy female and male controls ($n = 10$ each), being more prominent in male patients. Differences between (+), within (⋆) the groups and compared to controls (⋆) are rated significant at $p < 0.05$ (ANOVA on ranks)

isoflurane, plasma glutamate concentrations were significantly increased in discectomized patients compared to pre- anesthesia levels and healthy controls (Fig. 1). This increase was mostly sustained in male patients which remained elevated during the entire period of anesthesia.

Similar changes were seen in the electively craniotomized patients receiving isoflurane, again with a sustained increase in male patients (males: 121 ± 15 vs. females: $71 \pm 8\,\mu M$; $p < 0.01$) (Fig. 2). Within three hours after stopping isoflurane anesthesia, plasma glutamate concentrations decreased to lower values approaching control levels in female (68 ± 7 vs. $46 \pm 10\,\mu M$) and male patients (79 ± 9 vs. $52 \pm 7\,\mu M$) (Fig. 2).

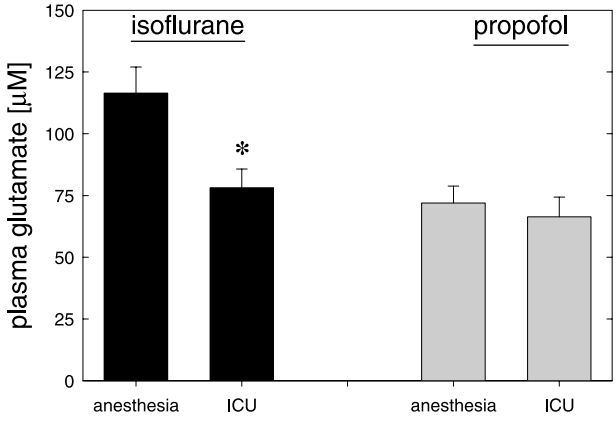

Fig. 2. Changes in plasma glutamate concentrations during isoflurane and propofol anesthesia in electively craniotomized patients. Plasma glutamate reached maximal levels at approximately 2 hours after initiation of isoflurane anesthesia followed by a significant decrease upon arrival at the intensive care unit (ICU), approximately 3 hours after cessation of anesthesia ($^{*}p < 0.05$, *t*-test). In patients receiving propofol, plasma glutamate concentrations remained unchanged at 2 hours upon arrival at the ICU compared with levels determined during anesthesia

During and after propofol anesthesia, plasma glutamate concentrations were significantly increased compared to controls and remained unchanged ranging from 65 to 87 µM, without any difference between male and female patients.

Overall, the significant increase in plasma glutamate was more prominent during isoflurane compared with propofol anesthesia (mean: 116 ± 11 vs. $72 \pm 7\,\mu M$; $p < 0.05$).

CSF glutamate concentrations

Compared with lumbar CSF samples taken from diagnostic lumbar puncture in ''control'' patients ($1.2 \pm 0.1\,\mu M$) [14], cranial CSF glutamate was significantly increased in all investigated craniotomized patients. This increase was more prominent in isoflurane-anesthetized patients with pre-existing vasogenic edema formation (Fig. 3).

Calculated CSF to glutamate ratio

The CSF to plasma ratio was only significantly increased in isoflurane-anesthetized patients with underlying edema formation compared with patients without contrast extravasation receiving isoflurane and all propofol-anesthetized patients with and without edema (Fig. 3).

Influence of plasma on CSF glutamate

Linear regression analysis revealed a significant increase in CSF glutamate depending on the corresponding

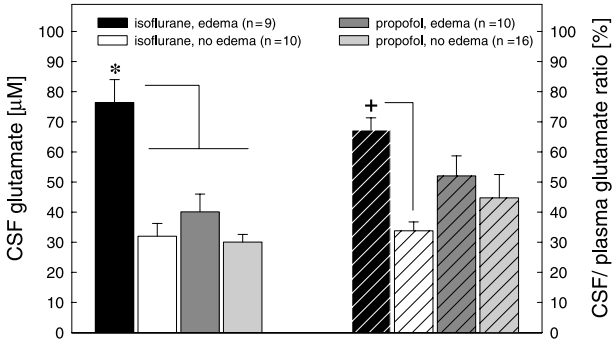

Fig. 3. At 120 ± 12 minutes after induction of anesthesia, paired plasma and CSF samples were taken upon opening of the dura. CSF glutamate was significantly increased in isoflurane-anesthetized patients with vasogenic edema formation compared to patients without contrast extravasation receiving isoflurane or propofol ($^{*}p < 0.005$; ANOVA on ranks). The calculated CSF to glutamate ratio (hatched bars) was only significantly increased in isoflurane-anesthetized patients with underlying vasogenic edema formation compared with isoflurane-anesthetized patients without edema ($^{+}p < 0.02$; ANOVA on ranks)

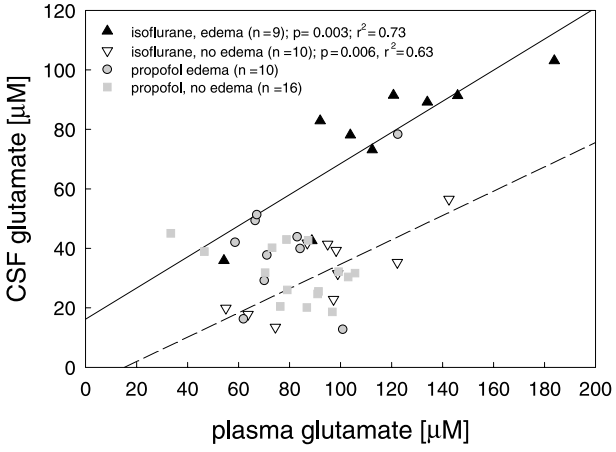

Fig. 4. Linear regression analysis of CSF and plasma glutamate. CSF glutamate was only significantly increased by plasma glutamate in isoflurane-anesthetized patients, which was more prominent in those patients with underlying vasogenic edema formation. In propofol-anesthetized patients, CSF glutamate was not influenced by plasma glutamate

plasma glutamate concentrations in all isoflurane-anesthetized patients (Fig. 4). This was more pronounced in patients with underlying vasogenic edema formation: isoflurane with edema: $CSF = 16.2 + (0.52 \times plasma)$, $n = 9$, $r^2 = 0.73$, $p = 0.003$; isoflurane without edema: $CSF = -6.2 + (0.41 \times plasma)$, $n = 10$, $r^2 = 0.63$, $p = 0.006$. In contrast, there was no significant relationship between CSF and plasma glutamate in propofol-anesthetized patients, regardless of preoperative contrast extravasation.

In vitro dilution experiment

Diluting plasma samples by 25, 50, and 75% with Diprivan® resulted in a similar relative decrease in plasma glutamate as seen when diluting with saline solution (data not shown).

Discussion

During routine isoflurane (Forane®) anesthesia, plasma and CSF glutamate were significantly increased in electively discectomized and craniotomized patients. These elevations were most prominent in male patients and craniotomized patients with pre-existing edema formation. The changes in plasma and CSF glutamate during propofol (Diprivan®) anesthesia were less pronounced compared with isoflurane anesthesia.

These findings are in line with recently published results obtained under experimental conditions where isoflurane was associated with a significant and reversible increase in plasma and CSF glutamate levels, NMDA receptor binding, EEG activity, and brain edema formation [37].

Based on experimental studies revealing a significant increase in edema formation upon elevating plasma glutamate concentrations by intravenously infusing glutamate [19], any increase in plasma glutamate is feared for its toxic potential and therefore, should be avoided. An elevation in plasma glutamate is of concern whenever the BBB is damaged and a passive penetration of the otherwise protected brain cannot be excluded. The significant increase in the calculated CSF to plasma glutamate ratio in patients with a disturbed BBB compared to those with an intact BBB suggests a dose-dependent penetration of the cerebral compartment. This warrants further investigation.

Under normal conditions, glutamate concentrations are very low within the cerebral extracellular space, ranging from 2 to 5 µM [27] while significantly higher levels are found within synaptic vesicles (up to 100 mM) [4] and plasma (50 µM) [39]. Consequently, this distribution pattern leads to a strong passive gradient directed from synapses and plasma towards the extracellular space. This, in turn, makes a tight regulation of release and uptake of this excitatory transmitter indispensable to prevent uncontrolled neuronal excitation [27]. Under pathological conditions, increased extracellular glutamate levels related to excessive release, abnormal leakage from neuronal and glial cytosol, or disturbed uptake can induce structural and functional deterioration by activating ionotropic and metabotropic glutamate receptors. Resulting derangement of ionic homeostasis, involvement of second and third messenger systems, production of oxygen free radicals and perturbation of energetic stability are signs of glutamate-mediated excitotoxicity, possibly leading to reduced glial and neuronal uptake of glutamate, reversal of glutamate transport, synaptosomal and cytosolic leakage of glutamate, and increased neuronal vulnerability [29]. While glutamate concentrations exceeding 100 µM have been shown to induce neuronal damage under *in vitro* conditions using mixed neuronal-glial cultures [33] and under *in vivo* conditions following injection of glutamate in the intact rat cortex [13] it remains unclear which glutamate concentrations are required to induce comparable neuronal and glial damage in humans. Experimental studies have convincingly shown that an underlying injury predisposes to further damage as reflected by sustained increase in edema formation and extracellular glutamate levels when subjecting traumatic brain-injured rats to additional global ischemia [1]. It also appears that

underlying structural and functional cellular impairment as observed following experimental traumatic brain injury could lower the threshold for glutamate-induced cerebral damage as additional injection of 100 μM glutamate significantly aggravated underlying brain damage [9].

Methodological considerations

The reported changes in plasma and CSF glutamate concentrations determined during isoflurane and propofol anesthesia were gathered prospectively in an open and descriptive study, investigating possible effects of routinely employed anesthesia on circulating glutamate. With an easier interpretation of results obtained in the discectomized patients due to similar underlying neuropathology and comparable baseline plasma glutamate levels seen in healthy controls, CSF glutamate levels in the craniotomized patients are more difficult to discuss due to the heterogeneity of the underlying brain tumors related to malignancy, tumor location, size, and growth rate. In this context, malignant brain tumors are also associated with disturbed glutamate uptake mechanisms [42], elevated extracellular glutamate concentrations [35], and glutamate-mediated excitotoxic injury responsible for the tumor progression [38]. These pathological alterations and the lack of pre-anesthesia CSF levels in the same patients as well as appropriate control cranial CSF values obtained by the same technique without anesthesia from healthy patients does not allow us to determine if baseline glutamate levels were elevated and to what extent the employed anesthesia increased CSF to plasma glutamate and influenced the calculated CSF to glutamate ratio in these patients. Other electively anesthetized patients without any neuropathology in whom lumbar CSF can be determined before, during, and after anesthesia might resolve this important issue. Using glutamate levels measured in CSF collected by lumbar puncture as reference values is of limited value as we cannot exclude a concentration gradient from the cranial to the lumbar level.

In these electively anesthetized and craniotomized patients isoflurane was combined with nitrous oxide known for its supplementary anesthetic potential as it inhibits glutamatergic transmission and thus allows one to reduce isoflurane concentration under clinical conditions. Whether nitrous oxide might have interfered with glial and neuronal glutamate uptake and release possibly accounting for the observed increase in CSF glutamate cannot be assessed by the present study or the literature available to date. Further experimental investigations are warranted.

Despite our *in vitro* testing allowing us to exclude a significant interference of the lipid solution of propofol on plasma amino acid levels during propofol anesthesia, we cannot exclude a metabolically relevant influence of the infused lipids. Based on the higher energetic potential of lipids compared to amino acids, the unchanged plasma glutamate concentrations might reflect diminished protein catabolism and would be a sign of a blunted metabolic stress response.

Systemic effects of anesthesia on plasma glutamate

The significant increase in plasma glutamate seems to be a rather unspecific effect, possibly related to decreased uptake, sustained release or attenuated renal elimination. The exact reasons for these changes, however, cannot be defined by the present study. Our results, however, are in line with findings reported by Horber and colleagues [17] and Carli and coworkers [5] who showed that halogenated volatile anesthetics significantly and reversibly increase plasma levels of essential and non-essential amino acids. Possible reasons for these elevations are seen in changed organ perfusion and overall metabolism. For isoflurane, decreases in intestinal [15] and renal perfusion combined with an attenuated glomerular filtration [24], increased proteolysis [17, 18] and reversible inhibition of hepatic mitochondiral respiratory chain [27] have been reported. As for propofol, reduced hepatic perfusion [16] and attenuated hepatic mitochondrial uptake of glutamate [14] have been observed. Thus, the increased plasma glutamate levels could be related to diminished hepatic metabolism as the liver is the most important organ for uptake and metabolism of blood-borne glutamate [41]. Renal perfusion and glomerular filtration, however, remain preserved during propofol anesthesia [23].

Local cerebral influence of anesthesia on CSF amino acids

Adequate evaluation of the increased CSF to plasma glutamate ratio is hindered by the fact that for ethical and technical reasons we cannot determine physiological cranial CSF to plasma glutamate ratio in healthy patients. A comparison with CSF to plasma glutamate ratio values based on lumbar CSF samples could in theory over- as well as underestimate the present findings

as we do not know whether glutamate remains elevated throughout the entire CSF space or is absorped and thus decreased on its passage from the brain to the lumbar region. However, linear regression analysis revealing a strong influence of corresponding plasma concentrations on elevated CSF glutamate levels suggests that the isoflurane-induced increases in glutamate results in a marked penetration of the central compartment, especially when a radiologically assessable BBB damage is present. A penetration of glutamate via a damaged BBB has been shown when injecting L-(N-13) glutamate used to determine recurrent growth of malignant brain tumors [33]. These findings suggest that brain tumors compromise the prevention of uncontrolled passage of plasma glutamate by the intact BBB [31] and off-set the stabilizing funtion of isoflurane on cerebral endothelial cells [6].

In addition to passive entry of plasma glutamate via an underlying damaged BBB, the encountered increases could also be induced by local isoflurane- and propofol-mediated functional alterations. Neuronal glutamate uptake and release processes are potential targets for the anesthetic action of isoflurane and propofol. Isoflurane has been shown to inhibit release of glutamate [22, 25, 32] without influencing uptake mechanisms [29]. Propofol has been reported to reduce uptake of glutamate [14] without limiting neuronal glutamate release [3, 14]. Furthermore, anesthetics have been shown to reversibly block mitochondrial function by inhibiting oxidation of glutamate which, in turn, results in diminished consumption of glutamate [27].

Apart from these outlined changes, isoflurane has also been held to interfere with amnestic and cognitive functions as it impairs spatial memory in naïve rats [7] and causes transient alteration in nocturnal sleep in humans [26]. Comparable studies, however, have not yet been conducted investigating propofol.

Conclusion

Further studies investigating the effects of other anesthetic agents on plasma and CSF glutamate levels are warranted to possibly identify the anesthetic regimen with the least possible adverse side-effects in terms of elevated plasma or CSF glutamate levels for neurosurgical patients known to already suffer from compromised cerebral homeostasis. Furthermore, structural and functional outcome studies are required to determine if these observed biochemical alterations might induce clinically relevant consequences.

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