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EDITORIAL COMMENT

An Emerging Malignant Arrhythmia Epidemic Due to Loperamide Abuse

Underlying Mechanisms and Clinical Relevance*

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LOPERAMIDE ABUSE AND CARDIOTOXICITY: A GROWING EPIDEMIC

The ability of psychoactive medications to cause electrophysiological toxicity and malignant cardiac arrhythmias has been recognized for >50 years (1). Typical manifestations include conduction slowing and/or QRS prolongation, QT prolongation, and ventricular tachyarrhythmias. Loperamide is a μ-opioid agonist that "is considered nonabsorbable: only insignificant amounts reach the systemic circulation and even less penetrate the blood-brain barrier. Therefore, at recommended dosages, the drug lacks central opioid-like effects" (2). However, this widespread belief is clearly inaccurate; at larger doses, loperamide is capable of producing substantial central nervous effects, and because of its low cost and widespread availability, it is rapidly becoming a significant drug of abuse. As loperamide abuse has risen, an increasing number of cases of loperamide-induced cardiotoxicity have been reported. The first such description was published in November 2014 (3). Since then, there have been at least 9 additional reports (4–12), of which 5 were published or in press in 2016.

The features of loperamide cardiotoxicity are fairly consistent (3–12). The cases all feature various combinations of QRS and/or QT prolongation, along with malignant arrhythmias, evidence of reduced excitability, and marked conduction disorders. Lethality is not rare. What mechanisms underlie these manifestations and what can be done about them?

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MECHANISMS OF LOPERAMIDE CARDIOTOXICITY: ION-CHANNEL BLOCKADE

In this issue of *JACC: Clinical Electrophysiology*, Klein et al. (13) present an elegant analysis of the possible ionic mechanisms that underlie loperamide cardiotoxicity. They examined the concentration-dependent effects of the drug on the human ether-a-go-go related channel (hERG, which corresponds to the delayed rectifier potassium [K^+]-current I_{Kr}) expressed in Chinese hamster ovary cells. I_{Kr}-block is by far the most common mechanism of drug-induced long-QT syndrome (LQTS) and Torsades de pointes (TdP) arrhythmias (14). The investigators noted that loperamide potently blocks hERG currents, with a 50% inhibitory concentration (IC_{50}) of 40 nM. They also noted that loperamide prolongs action potential (AP) duration (APD) in pig ventricular cells, which is consistent with repolarization delay due to I_{Kr}-block. Although they did not see a statistically significant decrease in phase 0 upstroke velocity that might have suggested sodium (Na^+)-current (I_{Na}) block, they did note an attenuation of APD-prolonging effects at higher drug concentrations, which is a typical feature of mixed K^+-/Na^+-channel blockers.

Kang et al. (15) also recently published a study of the ion-channel blocking effects of loperamide. They expressed ion-channel subunits corresponding to I_{Kr} (hERG), I_{Ks} (KvLQT1/minK), and I_{Na} (Nav1.5) in human embryonic kidney cells to evaluate loperamide

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actions. Like Klein et al. (13), they noted potent hERG current block with an IC_{50} of 89 nmol/l. However, they also noted that loperamide causes substantial I_{Na}-block with an IC_{50} of 297 nmol/l and has little effect on I_{Ks}.

RELATIONSHIPS BETWEEN ION-CHANNEL BLOCKING ACTIONS AND CLINICAL FINDINGS

The clinical manifestations of loperamide cardiotoxicity are complex. Some cases have presented with relatively little QRS prolongation, marked QTc prolongation, and typical TdP (8). These are typical manifestations of I_{Kr}-block and/or APD-prolongation toxicity (14). However, others have displayed dramatic QRS prolongation, modest QT changes, reduced excitability, and/or monomorphic ventricular tachyarrhythmias with broad QRS complexes (7,12). These abnormalities are indicative of marked I_{Na}-block, which are well-characterized for other psychotropic drugs with Na^+-channel blocking properties (16).

The findings reported by Klein et al. (13) provide insight into the LQTS presentation of loperamide toxicity, which are entirely compatible with the noted I_{Kr}-blocking effects (14). By contrast, the cases of marked conduction slowing, reduced excitability, and monomorphic tachyarrhythmias are not consistent with the effects of I_{Kr}-blockade. These cases likely reflect excess I_{Na}-block, as might be expected from the findings of Kang et al. (15).

CHALLENGES IN TRYING TO RELATE ION-CHANNEL BLOCKADE OBSERVATIONS TO CLINICAL PHENOMENA

Although the results of preclinical studies like those of Kang et al. (15) and Klein et al. (13) are consistent with the clinical manifestations of loperamide cardiotoxicity and likely account for them, readers should be aware of the challenges in translating voltage clamp studies in heterogenous expression systems to clinical observations.

The concentration dependence of effects is an important consideration. Sufficient electrophysiological changes to cause proarrhythmias are rarely seen before ~50% of the channels are blocked. For the studies by Kang et al. (15) and Klein et al. (13), that would be at concentrations of ~40 to 90 nmol/l for I_{Kr} and 300 nmol/l for I_{Na}. Plasma loperamide concentrations in overdoses can be as high as 120 to 140 ng/ml (6,11) or ~240 to 280 nmol/l, which would seem to suggest that the channel-blocking effects observed can explain the clinical manifestations. However, there is another crucial consideration. It is only the free drug (i.e., drug that is not protein-bound) in the plasma that is in equilibrium with extracellular drug concentrations and with target receptor sites on channels. Loperamide is ~97% protein-bound in plasma (17), meaning that free drug concentrations in overdose settings are at most 8 nmol/l. This value is not even close to the lowest experimental IC_{50} of 40 nmol/l reported by Klein et al. (13) for I_{Kr}. How then can the drug cause the significant electrophysiological effects noted?

The answer likely lies in the differences between key factors that govern ion-channel block in the clinical setting versus in the in vitro models used to study ion currents. The most important of these is the fact that drug block depends critically on the transmembrane potential, develops at depolarized (positive) potentials, and disappears over time at polarized (negative) potentials (18,19). This property makes channel block sensitive to heart rate and AP morphology (18). For technical reasons, in vitro patch-clamp experiments use square-wave voltage pulses (which only vaguely resemble APs) and frequencies that are often unphysiologically slow and produce much less block than in vivo (18,19). In addition, the conditions of intra- and extracellular solution composition and temperature needed to study the current of interest can have major effects on channel block. In studies of purified ion-channel subunits expressed in model cell systems, like those of Klein et al. (13) and Kang et al. (15), key ion-channel subunits modulating channel properties and drug block may be missing (19). By contrast, studies of native cardiomyocytes require additional conditions to isolate the current of interest from the many contaminating currents present, including the use of blockers, additional modifications to intra- and/or extracellular solutions, and unphysiological voltage protocols to isolate the current of interest. Thus, while the results of voltage-clamp studies are important and relevant, they must be interpreted carefully in order to be related realistically to the clinical context.

CLINICAL RELEVANCE OF ION-CHANNEL BLOCKADE OBSERVATIONS

Because of the preceding limitations, it is reasonable to ask whether studies of ion-channel blockade by clinically used compounds are of any real value. The answer is that they are, provided they are interpreted carefully. With appropriate precautions, it is possible to make precise correlations between ion-channel blocking observations in vitro and clinically relevant phenomena in vivo (16,20).

The findings by Klein et al. (13) and Kang et al. (15) explain the typical cardiotoxic features of loperamide overdoses quite well. The fact that some patients predominantly manifest the consequences of I_{Kr}-block (LQTS, TdP), whereas others predominantly manifest the effects of I_{Na}-block (QRS widening, monomorphic ventricular tachycardia, impaired excitability), likely relates to pharmacodynamic factors that modulate individual patient ion-channel sensitivity to drug block. Such factors can be acquired (e.g., heart rate, serum K^+-concentration, and other channel-blocking drugs) and congenital (in particular, genetic factors that govern drug sensitivity) (14), and can differentially affect the sensitivity of specific ion channels.

In addition to helping us understand the basis of the clinical manifestations of loperamide cardiotoxicity, the channel-blocking insights from basic studies can help to develop effective prevention. One might ask why a drug with narcotic abuse potential that causes lethal cardiotoxicity is freely available as an over-the-counter drug. Perhaps regulatory agencies should seriously consider restricting the availability of loperamide. Furthermore, with modern drug screening and development techniques, it should be possible to modify the loperamide structure to decrease the channel-blocking effects. This could be an interesting approach to develop new antidiarrheal agents that lack the cardiovascular risks associated with loperamide.

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