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Luminal K+ channels blocker: A superior therapeutic intervention over zinc in secretory diarrhea

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Trans-epithelial secretion and absorption of fluid and electrolytes across the intestinal epithelium is necessary for maintaining intestinal homeostasis. During secretory diarrhea this homeostasis has been altered, secretion is predominating over the absorption from the intestine. Massive loss of fluid into the intestinal lumen is driven by the active transport of ions, predominately Na+, K+ and Cl-. Oral Rehydration Solution (ORS) is used to replace fluid losses and promote intestinal fluid absorption has been the primary therapy for infectious diarrheas. An effective electrogenic secretion of Cl- is only possible if luminal potassium channels KCa3.1 (KCNN4c) is activated. Thus potassium channel has gotten attention in respect to secretory diarrhea. Recently we have identified TRAM-34 an inhibitor of luminal potassium channel KCNN4c is very effective against secretory diarrhea caused by Cholera Toxin (CT) or Ace of V. cholerae, heat Stable enterotoxin (STa) of Entero Toxigenic E. coli [ETEC], NSP4 enterotoxin of rotavirus that stimulates in vivo second messenger mediated Cl- and fluid secretion. In vitro experiments with mouse intestinal tissue in using chamber showed that luminal addition of TRAM-34 significantly abolished cAMP-stimulated short-circuit current (Isc), a reflector of active Cl- secretion. Whereas luminal addition of zinc did not have any effect on cAMP stimulated Cl- secretion but serosal addition of zinc causes immediate decrease of cAMP stimulated Cl- secretion in mouse tissue as well as human colonic T84 cell monolayers. In vivo mouse ileal loops experiment together with electrophysiological data suggests that mucosal addition of TRAM-34 dose dependently inhibit experimental diarrhea whereas zinc shows its activity when applied from serosal side. Moreover luminal application of TRAM-34 is equally effective against accessory cholera enterotoxin (Ace), heat-stable (STa) enterotoxin and NSP4 stimulated diarrhea. Thus a common K+ channel is to be involved in these enterotoxins stimulated Cl- secretion, which is inhibited by TRAM-34. Moreover toxicity study was performed in rabbit that shows TRAM-34 has minimal toxicity with the concentration ≈ 100 greater than used to block Cl- secretion. Thus TRAM-34 seems to be very effective and useful adjunct therapy than zinc along with ORS in secretory diarrhea.

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