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Title:

From Bench to Bedside: D-PLEX limits AMR occurrence in randomized double-blind phase 2 trial in colorectal surgery patients

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Despite significant advances in infection control guidelines and practices, surgical site infections (SSIs) remain a substantial cause of morbidity, prolonged hospitalization, and mortality. Among patients undergoing elective colorectal surgeries, SSI rates are particularly high, over 30%, due to the presence of intraluminal bacteria. While pre-operative systemic antibiotics reduce the SSI incidence, post operative exposure does not confer added protection, and application of local antibiotics-eluting-reservoirs do not seem to benefit patients undergoing colorectal surgeries.

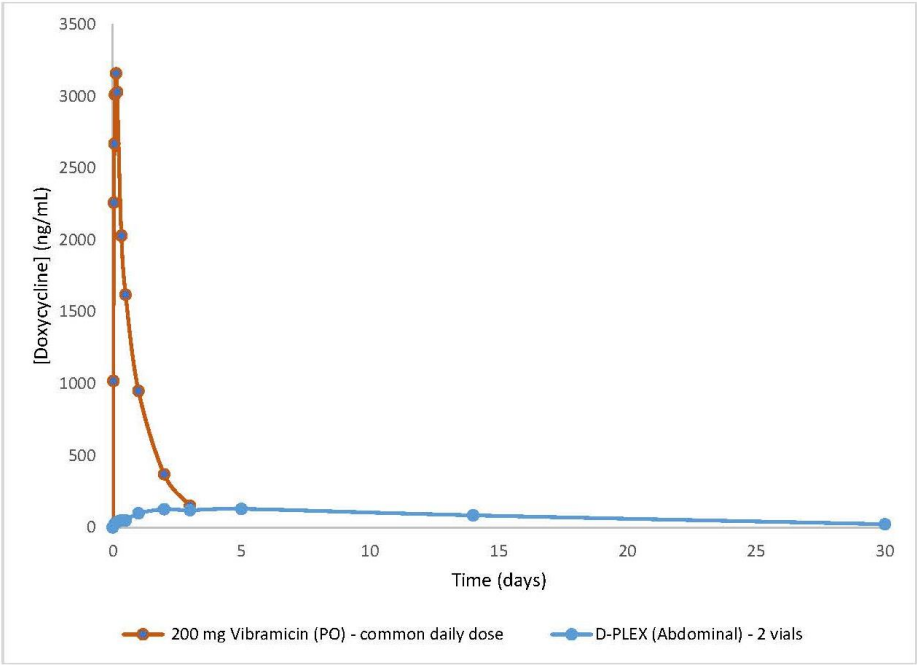
D-PLEX$_{100}$ is a novel, drug-eluting polymer-lipid matrix designed to be applied once directly at the surgical wound prior to wound closure. D-PLEX$_{100}$ uniquely releases a high, local concentration of doxycycline in a constant, zero order rate, for four weeks- a feature that was confirmed in vivo in custom designed SSI white rabbit models were local wound microdialysis pharmacokinetic (PK) parameters of doxycycline released from D-PLEX$_{100}$ (AUC and C_{max}) were analyzed and validated by HPLC-MS/MS. The in vivo results indicated robust and prolonged local exposure profile that is similar to the in vitro profile. Accordingly, in SSI prevention efficacy studies where animals were challenged with the most common gram-negative and gram-positive organisms and multi-drug resistant strains (doxycycline-resistant methicillin-resistance *Staphylococcus aureus* (MRSA) and *Klebsiella pneumoniae*), treatment with D-PLEX$_{100}$ resulted in statistically significant reduction of the challenged bacteria compared with the control placebo group **Table 1**. Notably, the SSI prevention efficacy tests also included organisms that are not indicated for the antibiotic doxycycline.

Table 1. Bacterial recovery summary in white rabbit SSI models

	Sternal model				Abdominal model				
Bacteria	Inoculum	Bacteria Count (CFU)			Inoculum	Bacteria Count (CFU)			P-Value
	Bacteria/site	Control	D-PLEX	Log10 Reduction	Bacteria/site	Control	D-PLEX	Log10 Reduction	
Enterobacter aerogenes (ATCC #13048)	1.2×10^8	$1.19*10^4$	39	3.47	1.2×10^7	$5.99*10^6$	1.79		<0.0001
Escherichia coli (ATCC #25922)	1.5×10^8	$7*10^8$	0	8.84				5.52	<0.0001
Klebsiella pneumoniae (ATCC #700603)	1.6×10^8	$5.7*10^5$	$4.05*10^3$	2.14					<0.0001
methicillin-resistant Staphylococcus aureus [MRSA ATCC #33591])	1.2×10^7	$9.74*10^8$	$7.74*10^5$	3.09	1.2×10^7	$3.55*10^7$	$8.66*10^3$	3.6	<0.0001
Staphylococcus epidermidis (ATCC #35984)	1.6×10^9	$4.2*10^4$	$7.52*10^2$	1.74					<0.0001
Enterococcus faecalis (ATCC 29212)	1.6×10^9	1.51×10^5	1.39×10^2	3.03					<0.0001
Vancomycin resistant Enterococcus faecium (ATCC #700221)					1.2×10^8	2.52×10^4	0	4.4	<0.0001

Animal safety histology studies indicated drastically reduced evidence of local necrosis in the D-PLEX$_{100}$ treated group compared to the untreated samples, and the plasma pharmacokinetic values in both animal models indicated negligible systemic exposure. The minimal systemic exposure was confirmed in patients treated with the maximum D-PLEX$_{100}$ dose (15g) where doxycycline exposure (mean C_{max}) was 183ng/mL, significantly lower than the 5,100ng/mL that was observed after a standard 200mg doxycycline oral dose (**Figure 1**).

Figure 1. Comparative mean plasma doxycycline concentration levels: D-PLEX vs. oral doxycycline.



Blood samples from 3 D-PLEX treated patients, 2 vials D-PLEX (109.2 mg), were assessed for plasma doxycycline concentration levels. Blood samples were collected for 30 days: at pre-dose (0), 2, 4, 6, 8, 12, 24 (Day 1), 48 (Day 2), 120 (Day 5), 336 (Day14) and 720 hrs (1 month) post-application of D-PLEX. The reference single oral administration is of Vibramicin (200 mg Doxycycline) as published by Gschwend et al 2007[29].

A phase II clinical trial in patients undergoing elective colorectal surgery evaluated SSI prevention by D-PLEX$_{100}$. Patients were randomized 1:1 to D-PLEX$_{100}$ plus Standard of Care (SOC) or SOC alone (**ClinicalTrials.gov identifier NCT03633123).** The SOC included prophylactic IV antibiotics 30-60 minutes prior to surgery, and D-PLEX$_{100}$ was applied based on the length of surgical incision (5-10 cm = 5g D-PLEX$_{100}$ (5g D-PLEX$_{100}$ contains 54.6 mg doxycycline), 11-20 cm = 10g D-PLEX$_{100}$, >20cm = 15g D-PLEX$_{100}$) at the time of surgical closure. The study results indicated a 64% reduction in SSI rate in the D-PLEX$_{100}$ plus SOC group (N=7/88 [7.9%]) vs SOC alone (N=20/91 [21.9%]); $p<0.05$. D-PLEX$_{100}$ was well tolerated and appeared to be free of serious adverse drug reactions.

Patients' bacterial colonization were also evaluated pre- and post surgery by rectal swab tests, and variations in the surgical wound microenvironment were assessed by isolating and identifying causative organisms within adjudicated postoperative soft tissue infection sites. There were no significant differences in colonization with multi-drug resistant organisms (MDROs) between groups based on rectal swabs. Causative organisms from SSI wounds were similar between study arms. The most common bacterial growth identified were related to the skin and colon normal flora; *Enterococcus Faecalis*, *Escherichia Coli*, *Pseudomonas Aeruginosa*, and *Staphylococcus Epidermidis*.

Positive SSI prevention results were also obtained in a small phase 1b/2 clinical trial in open heart surgery were D-PLEX$_{100}$ was applied directly on the sternum (**ClinicalTrials.gov identifier NCT03558984**).

Together, these data demonstrate that D-PLEX$_{100}$ is a safe and effective SSI prevention agent, and importantly, D-PLEX$_{100}$ activity was achieved without affecting the incidence of postoperative colonization by MDROs. As such, D-PLEX$_{100}$ may be a promising addition to established colorectal SSI bundles for reducing SSIs without the risks associated with systemic antibiotic exposure.