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# Irinotecan: Electron transfer mechanism in CNS disorders: Electron affinity, ROS, and SAR

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## Abstract

A recent article deals with promising use of irinotecan in treatment of Angelman Syndrome, a neurological disorder. The present report provides mechanistic evidence for involvement of electron transfer based on preliminary data from computational studies on electron affinity. The drug and the topotecan analog are related to camptothecin, a well-known anticancer drug. The protonated forms are better at electron affinity. Lactone hydrolysis may provide carboxyl for intramolecular protonation. The active phenol metabolits may also play a role. Structure-activity relationship (SAR) in addressed. These results buttress the prior hypothesis dealing with irinotecan mechanism in central nervous system toxicity.

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## Introduction

About a dozen years ago, a mechanism was proposed for the central nervous system toxicity by irinotecan (CPT-11) (Fig. 1) [1]. The proposal was an outgrowth of a report on the toxicity [2]. CPT-11, a semi-synthetic derivative of camptothecin (CTT) (Fig. 2), is used primarily in treatment of colon related cancer. Concerning the basic mode of action of CTT, much evidence exists for participation of electron transfer (ET), reactive oxygen species (ROS) and oxidative stress (OS) (3). Much of the rationale for mode of action is based on evidence from studies on the parent, anti-cancer drug CTT.

Many physiological responses involve bioactive substances or their metabolites which contain ET functional groups, such as quinones (or phenolic precursors), metal-containing substances, aromatic nitro compounds (or reduced metabolites) and conjugated imine or iminium species. The last category is the main focus of the present review. Schemes 1 and 2 portray redox cycling with generation of ROS. Redox cycling in vivo can occur when the ET agent has a reduction potential greater than -0.5 V which falls in the permissive range. A significant aspect is ROS concentration with higher levels producing toxicity and with lower levels being able to generate beneficial results.

Previous reports provide evidence for involvement of ROS, reactive nitrogen species (RNS), oxidative stress (OS) and antioxidants (AOs) in the bioactivation of anti-infective agents [4], anti-cancer agents [5], carcinogens [6], and toxins (toxicants) [7-19]. There is considerable evidence demonstrating that these unifying mechanistic concepts are applicable to the present review.

There is a plethora of experimental evidence supporting the theoretical framework, including generation of common ROS, lipid peroxidation, degradation products of oxidation, depletion of AOs, effect of exogenous AOs, DNA oxidation and cleavage of products, as well as electrochemical data.

This comprehensive, unifying mechanism is in keeping with the frequent observations that many ET substances display a variety of activities, *e.g.,* multiple drug properties, as well as toxic effects.

A recent report broadly links neurotoxicity to ET-ROS-OS [20], within which framework there is a fit with CTT serving as a model. ET can occur in the biodomain with CTT in protonated form according to electrochemical evidence [3]. The extensive conjugation of the radical anion favors stabiliaztion of the quinolinium ion which incorporates an attached planar structure. Pyridinuim aromatic character is associated with the N-alkyl-2- pyridone portion. Electrochemical data reveal that CTT in protonated form possesses a reduction potential amenable to ET in the biological milieu [3]. The quinolinium ion (iminium-like) is part of extensive conjugation, making for resonance stabilization of the ensuing radical. Regions of CTT associated with activity include the conjugated, planar, ring system which can be related to ET and site binding. The N-alkyl-2-pyridone portion displays aromatic character related to pyridinium.

The phenolic metabolite which has been designated the active form [1], has the same core structure capable of ET. Also, it may be a precursor of a quinone-imine structure analogous to that (Fig. 3) derived from ellipticines [5]. Several investigations link ET with antineoplastic activity of CTT [3]. A review on mechanism of anticancer drugs provides evidence of involvement of ET–ROS–OS [5]. ROS participation also appears to occur with CTT [3]. A number of reports indicate ROS involvement for CTT [3].

A 2011 article involves use of irinotecan in people with Angelman syndrome, a serious neurological disorder [21]. In a screening of 2306 compounds from drug libraries, CPT-11 was the only one which reactivates the Ube 3A gene and prevents DNA from unwinding. The mechanistic aspects are unclear. In the patients, the genetic defect results in speech loss, intellectual malfunction, balance and movement disabilities, excess laughter and excitable demeanor. In additional studies with

topotecan (Fig. 4), a structurally related anticancer drug, there are encouraging signs of a long-lasting effect in treatment of the CNS illness. Genes were associated with irinotecan pharmacokinetics in cancer patients [22].

Preliminary data are now provided to buttress the hypothesis in the form of computational studies involving electron affinity [EA]. Structure-activity relationship is discussed. Increasing evidence supports a multifaceted approach to drug action. Hence, it is reasonable to apply the ET-ROS-OS mechanism to CPT-11 action in Angelman Syndrome, which provides added support to the prior hypothesis [1].

## Electron affinity

The electron uptake efficiency of an ET agent is strongly correlated to its electron affinity (EA). Electron affinity is usually expressed as the inverse enthalpy change (-ΔH) for the process A+e- A-. The electron uptake is determined by the free energy (ΔG) for this electron attachment, which is related to the EA at any given temperature (T) by ΔG= ΔH-T ΔS = EA -T ΔS (ΔS= entropy change). However, because ΔS for this process is roughly independent of the electron acceptor (A), the free energy for the electron uptake is determined almost entirely by the EA. Electron affinities for many organic electron acceptors were obtained by directly measuring electron absorption coefficients in electron-rich environments.

Prior EA values are available [23] for prominent ET functionalities, such as quinones (0.54-0.64 eV) and aromatic nitro compounds (0.59 eV for dinitrophenol). EA values were also calculated for amphotericin B, a macrolide polyene antibiotic. The drug, which incorporates seven conjugated alkene moieties, gave EA values of 1.30 to 1.63 eV for the two conformers that are more favorable than the other ET agents cited above.

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We have calculated the gas-phase EA of irinotecan using density functional calculations, in order to establish whether it is likely to serve as a viable ET agent. Calculations were carried out using the B3LYP method and Dunnings's cc-pVDZ basis set [24-26], running under Gaussian 09 [27] on a Linux cluster. We determined EA values of 1.5 eV for neutral irinotecan and 5.4 eV for its protonated form at 298 K. The G values are predicted to differ from the H values by less than 0.1 eV.

Considerable attention has been devoted to metabolism, including hydrolysis of the lactone and sidechain ester portions of CTT and analogs catalyzed by esterases [28-50]. There is scant discussion of mechanistic impact. A hypothesis is presented herein concerning the role in bioactivity. An article a few years ago states that the key structural requirement for the antitumor activity in 10-hydroxycamptothecin is the intact lactone moiety [28]. Potent antitumor activity of the camptothecin class is known to be lost upon opening of the lactone ring [29]. In view of the above discussion, it may be that the open ring metabolites, although active, cannot reach the active site due to unfavorable pharmacokinetics or in inactive carboxylate, rather than carboxyl form. Various articles document the favorable influence of lactone hydrolysis. Carboxyesterases form active metabolites from this class by ring opening, resulting in potent inhibition of topoisomerase I [30-47].

According to our hypothetical approach, the conjugated polynuclear system plays a key role in ET. The EA calculations (see above) indicate that the protonated form of this entity operates much better in electron attraction than the parent base. Hence, it is conceivable that lactone ring opening provides a proton for intramolecular cation generation from the basic quinoline portion. The proton might be donated by the carboxyl group from hydrolysis. Alternatively, if lactone cleavage is catalyzed by proton, followed by nucleophilic attack by water, nitrogen cation formation may involve protonated carboxyl. A conformation illustrated in Fig. 5 shows the carboxyl hydrogen in close proximity to the lone pair electrons of quinoline nitrogen. The primary hydroxyl may hydrogen bond with amide

carboxyl, thus increasing aromaticity of the N-heterocylce. The tertiary-alcohol may hydrogen bond with carboxyl carbonyl. The phenolic metabolite (37, 38), potential precursor of iminoquinone (Fig. 3) has been designated the active form (see above).

## Other Relevant Data

Cyclic voltammetry data, provided on analogous conjugated quinolinium salts, lent credence to the ET-ROS-OS approach (48). Related studies based on computation (49) and reduction potentials (50), involving benzodiazepines, support the ET-ROS-OS unifying mechanism.

## List of abbreviations

Irinotecan, CPT-11; electron transfer, ET; reactive oxygen species, ROS; oxidative stress, US; antioxidant, AO

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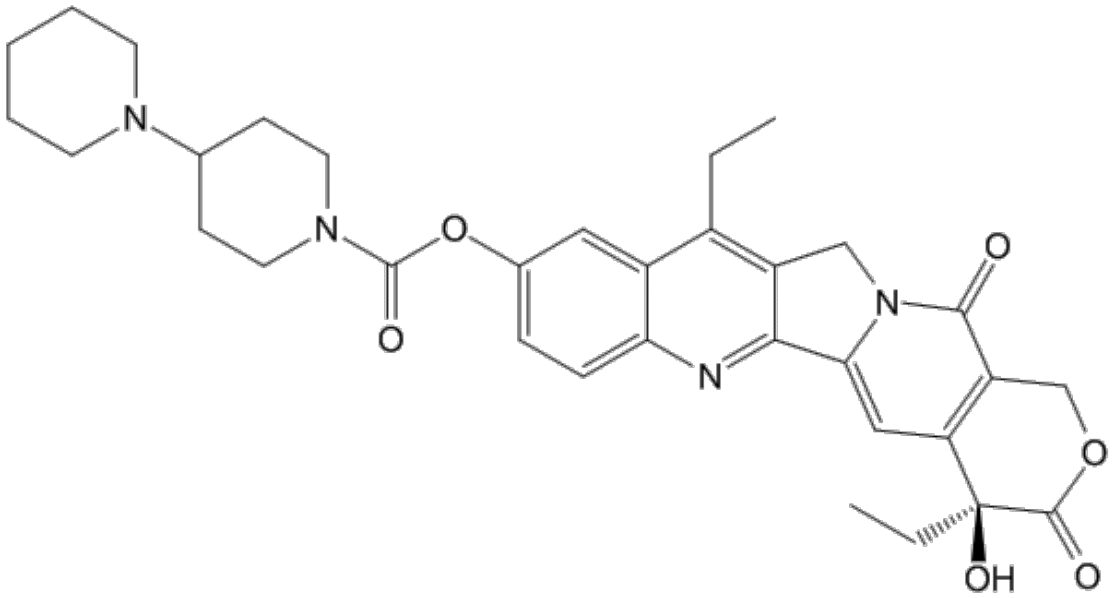


Fig. 1 CPT-11

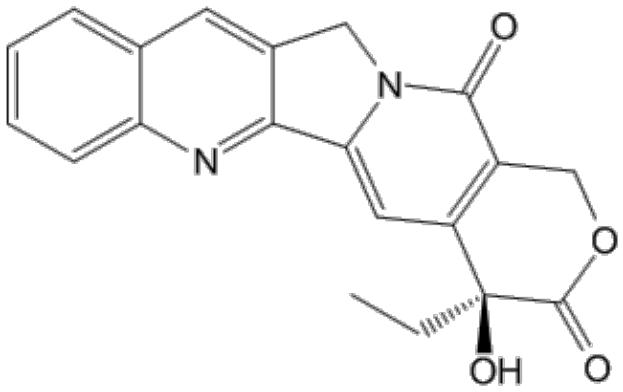


Fig. 2 CTT

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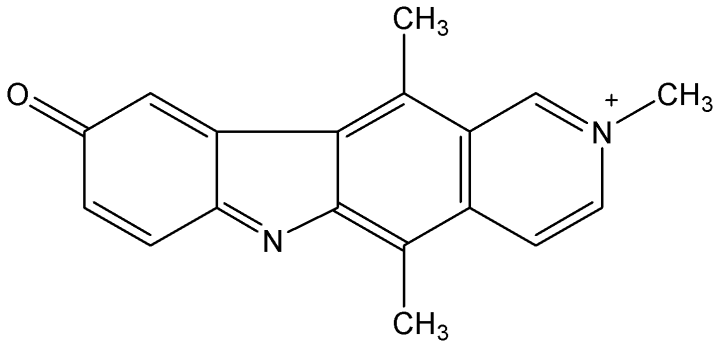


Fig. 3 Iminoquinone

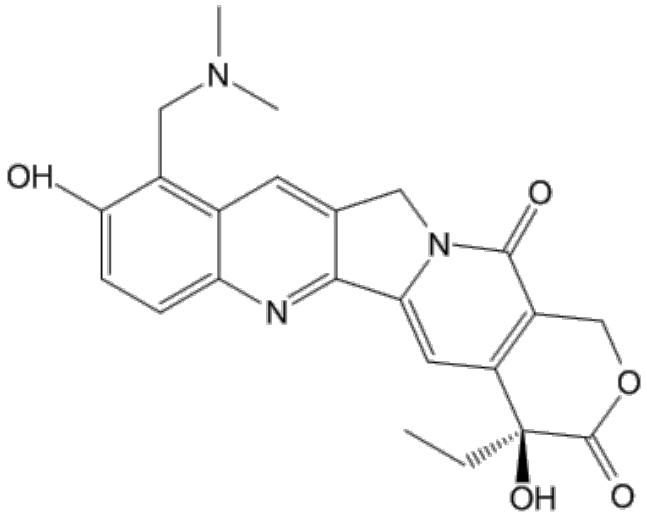


Fig. 4 Phenolmetabolite

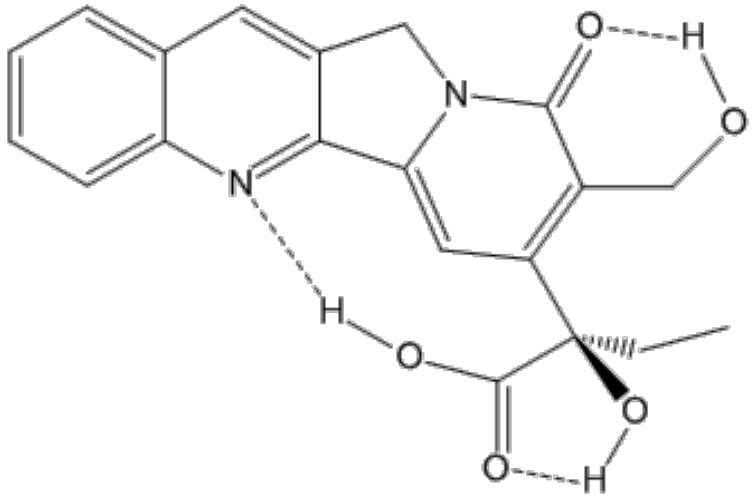


Fig. 5 Hydrogen bonding after lactone hydrolysis

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