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THE CLINICAL PHARMACOLOGY AND USE OF ANTIMICROTUBULE AGENTS IN CANCER CHEMOTHERAPEUTICS

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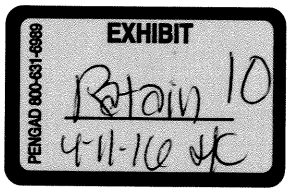
Abstract—Although there has been a rapid expansion of the number of classes of compounds with antineoplastic activity, few have played a more vital role in the curative and palliative treatment of cancers than the antimicrotubule agents. Although the vinca alkaloids have been the only subclass of antimicrotubule agents that have had broad experimental and clinical applications in oncologic therapeutics over the last several decades, the taxanes, led by the prototypic agent taxol, are emerging as another very active class of antimicrotubule agents. After briefly reviewing the mechanisms of antineoplastic action and resistance, this article comprehensively reviews the clinical pharmacology, therapeutic applications, and clinical toxicities of selected antimicrotubule agents.

CONTENTS

1. Introduction 36
2. Vinca Alkaloids 36
2.1. General 36
2.2. Mechanisms of action 37
2.3. Mechanisms of resistance 37
2.4. Vincristine 38
2.4.1. Clinical pharmacology 38
2.4.2. Dose and schedule 39
2.4.3. Clinical applications 40
2.4.4. Toxicities 43
2.5. Vinblastine 46
2.5.1 Clinical pharmacology 46
2.5.2. Dose and schedule 46
2.5.3. Clinical applications 46
2.5.4. Toxicities 49
2.6. Vindesine 50
2.6.1. Clinical pharmacology 50
2.6.2. Dose and schedule 51
2.6.3. Clinical trials 51
2.6.4. Toxicities 52
2.7. Vinorelbine (Navelbine) 53
2.7.1. Preclinical 53
2.7.2. Clinical pharmacology 54
2.7.3. Dose and schedule 54
2.7.4. Clinical trials 54
2.7.5. Toxicities 55
3. Taxanes 56
3.1. Taxol 56
3.1.1. Mechanisms of action 56
3.1.2. Preclinical antineoplastic activity 57
3.1.3. Mechanisms of resistance 58
3.1.4. Clinical pharmacology 58
3.1.5. Dose and schedule 59
3.1.6. Clinical trials 59



Abbreviations: ALL = acute lymphocytic leukemia; ANLL = acute nonlymphocytic leukemia; AUC = area under the time-versus-concentration curve; DNA = deoxyribose nucleic acid; GM-CFC = granulocyte-macrophage colony-forming cell; GTP = guanosine triphosphate; HSR = hypersensitivity reaction; MAPs = microtubule-associate proteins; NCI = National Cancer Institute; NVB = vinorelbine (Navelbine); SIADH = syndrome of inappropriate secretion of

3.1.7. Future directions 61
3.1.8. Toxicities 62
3.2. Taxotere (RP 56976) 65
3.3. Novel antimicrotubule agents in preclinical development and conclusion 65
References 66

1. INTRODUCTION

Microtubules are among the most strategic subcellular targets of anticancer chemotherapeutics. Like DNA, microtubules are ubiquitous to all cells. Although they are primarily recognized as being important in mitotic functions, microtubules also play critical roles in many interphase and maintenance functions in cells such as maintenance of cell shape and scaffolding, intracellular transport, secretion, and possible relay of signals between cell surface receptors and the nucleus (Edelman, 1976; Dustin, 1980; Crossin and Carney, 1981; Otto *et al.*, 1981). Interestingly, antimicrotubule agents are all structurally complex natural products or semisynthetic compounds. They are among the most important of anticancer drugs and have significantly contributed to the therapy of most curable neoplasms such as Hodgkin's and non-Hodgkin's lymphomas, germ cell tumors and childhood leukemia (Loehrer *et al.*, 1988b; DeVita *et al.*, 1989; Hellman *et al.*, 1989; Henderson *et al.*, 1990). They are also extremely useful in the palliative treatment of many other cancers. Despite their promise, only a few antimicrotubule agents have been developed over the last decade and only two vinca alkaloids, vincristine and vinblastine, are officially approved for use and are widely available for oncologic therapy in North America and Europe. However, there has recently been a resurgence of interest in these compounds. This has led to the identification and development of several novel vinca alkaloids like vinorelbine (Navelbine), as well as new classes of antimicrotubule agents such as taxanes, dolostatins, and rhizoxin which possess novel mechanisms of cytotoxic action, unique antitumor spectra *in vitro* and/or in the clinic, and potentially improved therapeutic indices. This review will focus on those vinca alkaloids and taxanes in which ample clinical and preclinical experience exists.

2. VINCA ALKALOIDS

2.1. General

The vinca alkaloids are natural or semisynthetic compounds which are present in minute quantities in the plant *Catharanthus roseus* G. Don (formerly *Vinca rosea* Linn.), commonly called the periwinkle. The compounds were originally screened by pharmaceutical chemists because of their use as hypoglycemic agents in several parts of the world. However, their hypoglycemic activity turned out to be of miniscule importance compared to their cytotoxic properties. Since the 1960s, only two vinca alkaloids, vincristine (VCR) and vinblastine (VBL), have been officially approved for the treatment of malignant disorders in the United States. Both VCR and VBL are large, dimeric compounds with similar but complex structures (Fig. 1). They are composed of an indole nucleus (the catharanthine portion) and a dihydroindole nucleus (the vindoline portion). VCR and VBL are structurally identical with the exception of the substitutent attached to the nitrogen of the vindoline nucleus where VCR possesses a formyl group and VBL has a methyl group. However, VCR and VBL differ dramatically in their antitumor spectrum and clinical toxicities.

A third vinca alkaloid analog, vindesine (VDS; desacetyl vinblastine carboxyamide), a synthetic derivative and human metabolite of VBL, was introduced into clinical trials in the 1970s. Although VDS has demonstrated activity against several malignancies, most notably non-small cell lung cancer, it has only been available for investigational purposes and its future is uncertain. Other vinca alkaloids with antitumor activity include vinleurosine and vinrosidine; however, further clinical development of these

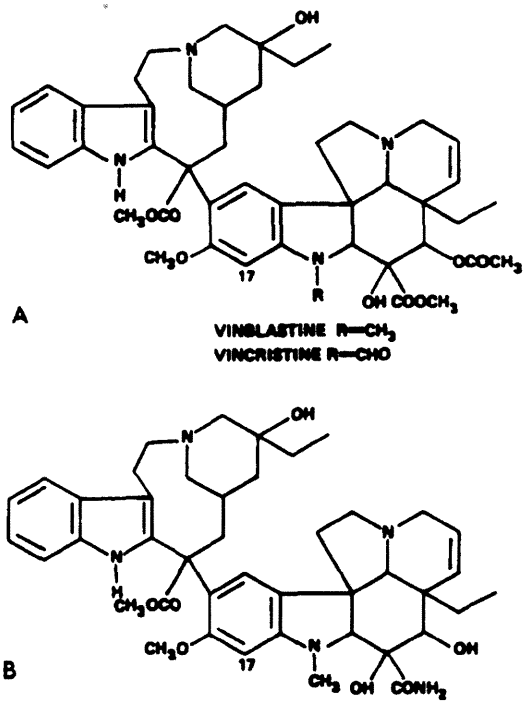


FIG. 1. Structures of vincristine and vinblastine (A); vindesine (B).

agents has been abandoned due to their exceptional toxicities (Creasey, 1975). Recently, semi-synthetic derivatives of VBL, specifically vinorelbine (Navelbine; NVB) and vinzolidine, have also entered clinical development and appear to be exciting for several reasons. These compounds, especially NVB, have demonstrated activity in neoplasms that are refractory to conventional agents. In addition, both NVB and vinzolidine are oral preparations in contrast to all other available vinca alkaloids which can only be administered by parenteral routes.

The clinical pharmacology, toxicology, and clinical applications of the vinca alkaloids, VCR, VBL, VDS, and NVB, will be discussed in this section. Relevant aspects of vinzolidine's clinical pharmacology and early phase I/II trials have been published (Budman *et al.*, 1984; Kreis *et al.*, 1986; Taylor *et al.*, 1990; Budman *et al.*, 1991). Extensive reviews of the identification, isolation, and characterization of the vinca alkaloids are also available (Johnson *et al.*, 1963; Neuss *et al.*, 1964; Creasy *et al.*, 1975).

2.2. Mechanisms of Action

The vinca alkaloids induce cytotoxicity by direct interactions with tubulin which is the basic protein subunit of microtubules (Johnson *et al.*, 1963; Olmstead and Borisy, 1973; Luduena *et al.*, 1977; Dustin, 1980). Other biochemical effects that have been reported for the vinca alkaloids include: (a) competition for transport of amino acids into cells; (b) inhibition of purine biosynthesis; (c) inhibition of RNA, DNA, and protein synthesis; (d) disruption of lipid metabolism; (e) inhibition of glycolysis; (f) alterations in the release of antidiuretic hormone; (g) inhibition of release of histamine by mast cells and enhanced release of epinephrine; and (h) disruption in the integrity of the cell membrane and membrane functions. Comprehensive reviews on these various effects have been published (Creasy, 1975, Beck, 1984).

Microtubules are ubiquitous in eukaryotic cells and vital to the performance of many critical functions including maintenance of cell shape, mitosis, meiosis, secretion, intracellular transport, and axonal transport. Many of the unique pharmacologic interactions of drugs with microtubules are due to a dynamic equilibrium between microtubules and tubulin dimers (Bryan, 1974; Dustin, 1980). Critical messages in the cell, including those related to cell cycle traverse, influence net microtubule polymerization. Vinca alkaloids exert their antimicrotubule effects by binding to a site on tubulin that is distinctly different from the binding sites of colchicine, podophyllotoxin, and taxol (Bryan, 1972a; Owellen *et al.*, 1972; Wilson *et al.*, 1975; Bhattacharyya and Wolff, 1976; Huang *et al.*, 1985). The vinca alkaloids bind to specific sites on tubulin with a binding constant of 5.6×10^{-5} M (Na and Timasheff, 1986) and initiate a sequence The binding of the vinca alkaloids to tubulin, in turn, prevents the polymerization of these subunits into microtubules. The subunits then form highly ordered paracrystalline arrays of tubulin that are often termed 'paracrystals' (Bryan, 1972b; Manfredi and Horowitz, 1984a) which contain one mole of bound drug per mole of tubulin (Bensch and Malawista, 1969). The net effects of these processes include the blockage of the polymerization of tubulin into microtubules which may eventually lead to the inhibition of vital cellular processes and cell death.

Although most evidence indicates that mitotic arrest is the principal cytotoxic effect of the vinca alkaloids, there is also evidence suggesting that the lethal effects of these agents may be attributable in part to effects on other phases of the cell cycle. The vinca alkaloids appear to be cytotoxic to nonproliferating cells *in vitro* and *in vivo* in both G_1 and S cell cycle phases (Madoc-Jones and Mauro, 1968; Strychmans *et al.*, 1973; Rosner *et al.*, 1975).

2.3. Mechanisms of Resistance

Resistance to the vinca alkaloids develops fairly rapidly *in vitro* in the presence of these agents. To date, two mechanisms of resistance have been described. The first mechanism involves mutations in either the alpha or beta subunits of tubulin, leading to decreased vinca alkaloid binding (Cabral *et al.*, 1986; Brewer and Warr, 1987). The second, more well characterized mechanism of resistance involves the general multi-drug resistance (mdr) phenotype that confers broad resistance to many unrelated classes of large, bulky natural product antineoplastic agents including the antitumor antibiotics, vinca alkaloids, colchicine, and taxol, and the epipodophyllotoxins (Juliano and Ling, 1976; Wilkoff and Dulmadge, 1978; Beck *et al.*, 1979; Riordan and Ling, 1979; Inaba *et al.*, 1984; Conter and Beck, 1984; Gupta, 1985; Beck, 1987; Fojo *et al.*, 1987a,b; Greenberger *et al.*, 1987; Hamada *et al.*, 1987; Choi *et al.*, 1988; Moscow and Cowan, 1988). Cells with mdr phenotype possess an increased capacity to expel natural products by virtue of increased amounts of membrane phosphoglycoproteins (P-glycoproteins) such as the P-170 membrane glycoprotein that functions as a drug efflux pump (Hamada *et al.*, 1987). A substantial number of unrelated compounds, including calcium channel antagonists (Tsuruo, 1983; Brewer and Warr, 1987), phenothiazines and other 'calmodulin antagonists' (Tsuruo *et al.*, 1983; Akiyama *et al.*, 1986), antiarrhythmic agents such as quinidine and amiodarone (Tsuruo *et al.*, 1984; Inaba and Earuyama, 1988), cephalosporins (Gosland *et al.*, 1989), and cyclosporin A (Slater *et al.*, 1986) have been demonstrated to reverse drug resistance related to the mdr phenotype. Interestingly, the ability of the calcium channel blocker verapamil or cyclosporin A

related to either calcium channel antagonism or immunomodulation since inactive isomers are considerably more active in reversing this type of resistance (Gruber *et al.*, 1988; Twentyman, 1988).

2.4. VINCRISTINE

2.4.1. *Clinical Pharmacology*

Relative to their broad clinical use, there are limited data available about the pharmacology of the vinca alkaloids in humans compared to other classes of antineoplastic agents. This has primarily been due to a lack of sensitive assays capable of measuring minute plasma concentrations which result from the wide distribution of mg doses of these agents. Early animal and human studies used radiolabeled vinca alkaloids, with further separation of parent drug and metabolites by high-pressure liquid chromatography (HPLC) (Castle *et al.*, 1976; Bender *et al.*, 1977; Culp *et al.*, 1977; El Dareer *et al.*, 1977; Owellen *et al.*, 1977a,b; Jackson *et al.*, 1978; Owellen and Hartke, 1985). More recently, studies using sensitive radioimmunoassays (RIA) and enzyme-linked immunosorbent assay (ELISA) methods, which may be able to detect picomolar concentrations, have been able to overcome these problems (Nelson *et al.*, 1979, 1980; Hande *et al.*, 1980; Jackson *et al.*, 1980, 1981a; Sethi *et al.*, 1981b; Sethi and Kimball, 1981; Nelson, 1982; Hacker *et al.*, 1984; Rahmani *et al.*, 1985; Labinjoki *et al.*, 1986; Ratain and Vogelzang, 1986, 1987).

Following standard doses of VCR administered as a bolus intravenous injection, peak plasma VCR levels approach 0.4 μM (Bender *et al.*, 1977). VCR's plasma distribution is characterized by triexponential kinetics with a distribution (alpha) half-life ($t_{\frac{1}{2}}$) of less than 5 min owing to extensive and rapid tissue binding. Beta phase $t_{\frac{1}{2}}$ values have been reported to range from 50 to 155 min and terminal $t_{\frac{1}{2}}$ values have varied even more profoundly, from 23 ± 17 to 85 ± 65 hr (Owellen *et al.*, 1977b; Nelson *et al.*, 1980; Jackson *et al.*, 1981b; Sethi *et al.*, 1981b; Nelson, 1982). Similar pharmacokinetic parameters have been noted in children (Sethi and Kimball, 1982). When the pharmacologic behavior of VCR has been studied using ^{3}H-VCR coupled with purification by HPLC, alpha, beta, and terminal $t_{\frac{1}{2}}$ have been determined to be 0.85, 7.4, and 64 min, respectively (Bender *et al.*, 1977). In one comparative pharmacokinetic study of VCR, VBL, and VDS, VCR had the longest terminal $t_{\frac{1}{2}}$, 85.0 ± 68.9 hr, versus 24.8 ± 7.5 hr for VBL and 24.2 ± 10.4 hr for VDS (Nelson *et al.*, 1980; Nelson, 1982). The apparent volumes of distribution (V_d) have also been high ($V_d$central of 0.328 ± 0.106 l/kg and $V_d$gamma, 8.42 ± 3.17 l/kg for VCR), indicating extensive tissue binding (Nelson *et al.*, 1980; Nelson, 1982). In addition, marked differences in serum clearance rates have been noted with VCR having the slowest clearance (0.106 ± 0.061 l/kg-hr), VBL the highest (0.740 ± 0.317 l/kg-hr), and VDS an intermediate value (0.252 ± 0.100 l/kg-hr) (Nelson *et al.*, 1980; Nelson, 1982). It has been postulated that VCR's longer terminal half-life and lower plasma clearance rate compared to other vinca alkaloids might account for its greater neurotoxic effects (Nelson *et al.*, 1980; Nelson 1982).

There has been a considerable interest in the administration of VCR on protracted continuous infusion schedules based on the likelihood that these schedules more closely simulate optimal *in vitro* conditions required for cytotoxicity compared to bolus schedules (Jackson, 1990). The cytotoxicity of the vinca alkaloids appears to be dependent not only on drug concentration, but on duration of treatment (Jackson and Bender, 1979; Hill and Whelan, 1980; Ferguson *et al.*, 1984; Ludwig *et al.*, 1984; Jackson, 1990). VCR concentrations in the range of 100 nM are only briefly achieved after intravenous bolus injections and levels typically decline to less than 10 nM by 2 to 4 hr approaching 1 nM by 48 to 72 hr (Nelson *et al.*, 1980; Jackson *et al.*, 1981b). When compared to conditions required for cytotoxicity *in vitro*, though, treatment with 100 nM VCR for 3 hr is required to kill 50% of L1210 murine or CEM human lymphoblastic leukemias, whereas 6 to 12 hr of treatment is required to achieve this degree of cytotoxicity at 10 nM and no lethal effects occurs with VCR concentrations below 2 nM (Jackson and Bender, 1979). Interestingly, a 0.5 mg intravenous bolus injection of VCR followed by a continuous infusion at doses of 0.5 to 1.0 mg/m^2/day for 5 consecutive days has typically produced steady-state VCR concentrations ranging from 1 nM to 10 nM and half-lives after discontinuation of the infusions have ranged from 10.5 hr (1.0 mg/m^2) to 21.7 hr (0.5 mg/m^2) (Jackson *et al.*, 1981b). Although peak VCR plasma concentrations achieved with continuous infusions have generally been lower than levels achieved with bolus injections, continuous infusions have produced greater total drug exposure above a critical threshold concentration (Jackson *et al.*, 1981b).

The tissue distribution of VCR has been investigated in several animal species. In the dog and the rat, the spleen appears to concentrate VCR to a greater extent than any other tissue (Owellen and Donigian, 1972; Castle *et al.*, 1976). In the monkey, the tissue with the highest VCR concentration has been the pancreas (El Dareer *et al.*, 1977). Although VCR has been demonstrated to rapidly enter the central nervous system of primates after intravenous injection, with VCR levels above 1 nM maintained in cerebrospinal fluid for longer than 72 hr in one study (El Dareer *et al.*, 1977), most investigations using rats, dogs, monkeys, and humans have indicated that VCR penetrates poorly through the blood–brain barrier (Castle *et al.*, 1976; El Dareer *et al.*, 1977; Jackson *et al.*, 1980, 1981a). In humans, cerebrospinal fluid levels have been 20- to 30-fold lower than concurrent plasma concentrations and have never exceeded

1.1 nM (Jackson *et al.*, 1981a). Approximately 48% of VCR is bound to serum proteins (Bender *et al.*, 1977). VCR also undergoes extensive binding to formed blood elements, especially platelets and red blood cells, which has led to the use of VCR-loaded platelets for treating disorders of platelet consumption such as idiopathic thrombocytopenia purpura (see Section 2.4.3, Clinical Applications).

VCR is primarily metabolized in the liver and excreted in the feces (Bender *et al.*, 1977; Jackson *et al.*, 1978). Within 72 hr after the administration of radiolabeled VCR, 12% of the total labeled material is excreted in the urine, 50% of which consists of metabolites; and approximately 70% is excreted in the feces, 40% of which consists of metabolites (Bender *et al.*, 1977). VCR rapidly concentrates in the bile with an initial bile : plasma concentration ratio of 100 : 1 which declines to 20 : 1 at 72 hr post-injection (Jackson *et al.*, 1978). Metabolic products accumulate rapidly in the bile such that only 46.5% of the total biliary product is the unmetabolized parent compound (Jackson *et al.*, 1978). Many studies in both man (Bender *et al.*, 1977, Jackson *et al.*, 1978, Sethi *et al.*, 1981a,b) and animals (Castle *et al.*, 1976, Houghton *et al.*, 1984) have demonstrated that approximately 6 to 11 metabolites are produced. The structures of all these metabolites have not been definitely identified; however, analytical studies of the products formed by incubating VCR with dog bile have identified 4-deacetylVCR as a principal metabolite (Sethi and Thimmaiah, 1985; Thimmaiah and Sethi, 1990). In addition, 4-deacetylvincristine (Houghton *et al.*, 1984) and *N*-deformylVCR (Sethi *et al.*, 1981a) have been isolated from human bile. 4'-Deoxy-3'-hydroxyVCR and 3',4'-epoxyvincristine *N*-oxide have also been tentatively identified from *in vitro* incubation of VCR with bile from dogs (Thimmaiah and Sethi, 1990).

2.4.2. *Dose and Schedule*

VCR is routinely administered to children as a bolus intravenous injection at doses of 2.0 mg/m^2 weekly (Livingston and Carter, 1970). For adults, the conventional weekly dose is 1.4 mg/m^2. A restriction of the absolute single dose of VCR to 2.0 mg/m^2 has been adopted by many clinicians over the last several decades, presumptively based on reports of exceptional neurotoxicity at higher doses. Nevertheless, the origin of this restriction has recently been investigated and felt to be largely based on empiricism (Sulkes and Collins, 1987). Available evidence suggests that this absolute restriction should be reconsidered (Sulkes and Collins, 1987). It has readily been appreciated that cumulative dose may be a more critical variable than single dose; however, wide interpatient variability exists and some patients are able to tolerate much higher VCR doses with little or no toxicity (Costa *et al.*, 1962, Holland *et al.*, 1973). This [illegible] significant individual differences in areas under the time-versus-concentration curves (AUC) which have been found to vary by as much as 11-fold (Desai *et al.*, 1982; Van den Berg *et al.*, 1982). However, this explanation does not justify capping VCR doses at 2.0 mg.

It is commonly believed that subsequent doses of VCR should be adjusted based on toxicity; however, doses should not be reduced for a mild peripheral neuropathy, particularly if VCR is being used in a regimen with curative intent. Instead, VCR may have to be held for signs and symptoms indicative of more serious neurotoxicity, including severe symptomatic sensory changes, motor and/or cranial nerve deficits, and ileus, until these toxicities resolve. In clearly palliative settings, more liberal attitudes about dose reduction or lengthening dosing intervals may be justified for moderate neurotoxicity.

Based on *in vitro* data indicating that the duration of VCR treatment above a critical threshold concentration is an important determinant for cytotoxicity (Jackson and Bender, 1979), phase I/II trials in adults have evaluated prolonged continuous infusion schedules (Jackson, 1990). Following a 0.5 mg/m^2 intravenous injection of VCR, total daily VCR doses of 0.25 to 0.50 mg/m^2 as a continuous infusion for 5 consecutive days have generally been well tolerated (Weber *et al.*, 1979; Hopkins *et al.*, 1983; Jackson *et al.*, 1984b, 1985a,b, 1986a; Pinkerton *et al.*, 1985; Yau *et al.*, 1985; Jackson, 1990). In pediatric patients, the continuous infusion of VCR for 5 consecutive days has permitted a twofold increase in the dose that could be safely administered without major toxicity compared to bolus administration schedules (Pinkerton *et al.*, 1988).

VCR is a potent vesicant and should not be administered intramuscularly, subcutaneously, or intraperitoneally. VCR has been accidentally administered into the cerebrospinal fluid resulting in rapid death (Slyter *et al.*, 1980; Gaidys *et al.*, 1983; Williams *et al.*, 1983; Dyke, 1989). VCR (0.4 mg/day for 5 consecutive days) has also been administered by the hepatic intra-arterial route to 6 patients with metastatic liver disease (colon cancer (5); non-Hodgkin's lymphoma (1)) (Jackson *et al.*, 1984c). No objective responses were observed, and toxicities, including substantial neurotoxicity (confusion, weakness, ileus, aphasia, postural hypotension, urinary incontinence), were very severe in some patients. Diarrhea, a rare toxicity of VCR on bolus schedules, was also observed in one third of the patients.

Although it has not been carefully evaluated, an apparently major role of the liver in the disposition and metabolism of VCR (see Section 2.4.1., Clinical Pharmacology) indicates that dose modifications should be considered for patients with hepatic dysfunction (Van den Berg *et al.*, 1982). To date, firm guidelines for dose modifications have not been established; however, a 50% dose reduction is often recommended for patients with plasma in bilirubin

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